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STUDIES ON EXPERIMENTAL HYPERTENSION

XV. EXPERIMENTAL OBSERVATIONS ON HYPERTENSION ASSOCIATED WITH UNILATERAL RENAL DISEASE; EFFECT OF OCCLUSION OF THE URETER ON EXPERIMENTAL HYPERTENSION DUE TO UNILATERAL RENAL ISCHEMIA

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LOS ANGELES

In the earliest studies on experimental hypertension due to renal ischemia [1] it was shown that constriction of the main artery of only one kidney in a dog or a monkey is sufficient to cause elevation of the blood pressure. It was also shown in these and in later studies [2] that this elevation does not usually persist indefinitely unless the other kidney is removed or unless the main artery of the other kidney is also constricted.

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1. (*a*) Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension: I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, J. Exper. Med. **59**: 347 (March) 1934. (*b*) Goldblatt, H.: Studies on Experimental Hypertension: III. The Production of Persistent Hypertension in Monkeys (Macaque) by Renal Ischemia, ibid. **65**:671 (May) 1937.

2. Goldblatt, H.: (*a*) Studies on Experimental Hypertension: V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, Ann. Int. Med. **11**:69 (July) 1937; (*b*) Experimental Hypertension Induced by Renal Ischemia, in Harvey Lectures, 1937-1938, Baltimore, Williams & Wilkins Company, 1938, pp. 237-275; Bull. New York Acad. Med. **14**:523 (Sept.) 1938; (*c*) Studies on Experimental Hypertension: XII. The Experimental Production and Pathogenesis of Hypertension Due to Renal Ischemia, Am. J. Clin. Path. **10**:40 (Jan.) 1940.

In most dogs with unilateral renal ischemia the blood pressure returns to the preoperative level in six weeks or less, but in some the hypertension may persist at a high level for many months. The return of the blood pressure to normal obviously may be due (*a*) to the development of considerable accessory circulation to the ischemic kidney or (*b*) to the compensating, neutralizing or inhibiting effect of the contralateral normal kidney. The way in which this mechanism acts is not yet known. In this connection, the significant observation was also made that if the single ischemic kidney is removed after a short or even a long period of hypertension the blood pressure usually returns to the preoperative level in twenty-four to forty-eight hours and remains at this level.[2a] These observations have all been fully confirmed by other investigators.[3]

The existence in man of hypertension associated with bilateral chronic pyelonephritis has been recognized [4] for some time. Recently an exhaustive treatise on the subject has been written.[5] The experimental production of hypertension by constriction of one main renal artery and the cure of the hypertension by removal of the ischemic kidney have led to the recognition of hypertension associated with unilateral chronic pyelonephritis in man as well as to the successful treatment of this condition by the removal of the diseased kidney when the other kidney is normal. In man, as in some dogs, the hypertension evidently may persist for a long time on the basis of unilateral renal disease. There have been reported cases of human hypertension associated not only with unilateral

3. (*a*) Wood, J. E., and Cash, J. R.: Experimental Hypertension: Observations on Sustained Elevation of Systolic and Diastolic Blood Pressure in Dogs, J. Clin. Investigation **15**:543 (Sept.) 1936. (*b*) Elaut, L.: Observations concernant l'hypertension chronique expérimentale du chien par constriction de l'artère rénale, Compt. rend. Soc. de biol. **123**:1244 (Nov.) 1936. (*c*) Page, I. H., and Sweet, J. E.: Extirpation of Pituitary Gland: Effect on Arterial Blood Pressure of Dogs with Experimental Hypertension, Proc. Soc. Exper. Biol. & Med. **34**:260 (March) 1936. (*d*) Blalock, A., and Levy, S. E.: Studies on the Etiology of Renal Hypertension, Ann. Surg. **106**:826 (Nov.) 1937. (*e*) Verney, E. B., and Vogt, M.: An Experimental Investigation into Hypertension of Renal Origin, with Some Observations on Convulsive "Uraemia," Quart. J. Exper. Physiol. **28**: 253 (Sept.) 1938. (*f*) Fasciolo, J. C.; Houssay, B. A., and Taquini, A. C.: The Blood Pressure Raising Secretion of the Ischemic Kidney, J. Physiol. **94**:281 (Dec.) 1938. (*g*) Gibson, J. G., II., and Robinson, R. W.: Blood Volume, Cardiac Size and Renal Function in Dogs with Hypertension Produced by Goldblatt Technic, Proc. Soc. Exper. Biol. & Med. **39**:497 (Dec.) 1938. (*h*) Katz, L. N.; Friedman, M.; Rodbard, S., and Weinstein, W.: Observations on the Genesis of Renal Hypertension, Am. Heart J. **17**:334 (March) 1939.

4. Löhlein, M.: Ueber Schrumpfnieren, Beitr. z. path. Anat. u. z. allg. Path. **63**:570, 1917. Longcope, W. T.: Chronic Bilateral Pyelonephritis: Its Origin and Its Association with Hypertension, Ann. Int. Med. **11**:149 (July) 1937.

5. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, Medicine **18**:221 (Sept.) 1939.

chronic pyelonephritis (with or without calculus) [6] but with unilateral vascular disease, including thrombosis and embolism, with or without infarction; kinking, anomaly or aneurysm of the main renal artery [7]; tumor of one kidney [8] and urinary obstruction due to a variety of patho-

6. (*a*) Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, J. Clin. Investigation **16**:889 (Nov.) 1937. (*b*) Barker, N. W., and Walters, W.: Hypertension Associated with Unilateral Chronic Atrophic Pyelonephritis: Treatment by Nephrectomy, Proc. Staff Meet., Mayo Clin. **13**:118 (Feb. 23) 1938. (*c*) Crabtree, E. G.: Hypertension in Destructive Infected Unilateral Lesions of the Kidney, Tr. Am. A. Genito-Urin. Surgeons **31**:299 (May) 1938. (*d*) Barney, J. D., and Suby, H. I.: Unilateral Renal Disease with Arterial Hypertension: Report of a Case Apparently Cured Following Nephrectomy, New England J. Med. **220**:744 (May 4) 1939. (*e*) McIntyre, D. W.: Unilateral Chronic Pyelonephritis with Arterial Hypertension, J. Urol. **41**:900 (June) 1939. (*f*) Nesbit, R. M., and Ratliff, R. K.: Hypertension Associated with Unilateral Nephropathy, ibid. **43**:427 (March) 1940. (*g*) Schroeder, H. A., and Fish, G. W.: Studies on "Essential" Hypertension: III. The Effect of Nephrectomy upon Hypertension Associated with Organic Renal Disease, Am. J. M. Sc. **199**:601 (May) 1940. (*h*) Braasch, W. F.; Walters, W., and Hammer, H. J.: Hypertension and the Surgical Kidney, J. A. M. A. **115**:1837 (Nov. 30) 1940. (*i*) Mulholland, S. W.: Hypertension's Challenge to Urology, J. Urol. **42**:957 (Dec.) 1939. (*j*) Engel, W. J.: Association of Unilateral Kidney Disease with Hypertension, Cleveland Clin. Quart. **7**:290 (Oct.) 1940. (*k*) Salley, S. M.: Hypertension Due to Unilateral Kidney Disease, Bull. Jackson Mem. Hosp. **3**:10 (Jan.) 1941. (*l*) Maher, C. C., and Wosika, P. H.: Urologic Hypertension: A Study of 101 Cases, J. Urol. **41**:893 (June) 1939. (*m*) Bothe, A. E.: Pyelonephritis in Children and Adults with Hypertension, ibid. **42**:969 (Dec.) 1939). (*n*) Patch, F. S.; Rhea, L. J., and Codnere, J. T.: Hypertension in a Girl of Twelve, Associated with Unilateral, Chronic, Atrophic Pyelonephritis Treated by Nephrectomy, Canad. M. A. J. **43**:419 (Nov.) 1940. (*o*) Kennedy, R. L. J.; Barker, N. W., and Walters, W.: Malignant Hypertension in a Child: Cure Following Nephrectomy, Am. J. Dis. Child. **61**:128 (Jan.) 1941.

7. (*a*) Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, Am. J. Path. **13**:679 (Sept.) 1937. (*b*) Leadbetter, W. F., and Burkland, C. F.: Hypertension in Unilateral Renal Disease, J. Urol. **39**:611 (May) 1938. (*c*) Boyd, C. H., and Lewis, L. G.: Nephrectomy for Arterial Hypertension, ibid. **39**:627 (May) 1938. (*d*) Blackman, S. S., Jr.: Arteriosclerosis and Partial Obstruction of the Main Renal Arteries in Association with "Essential" Hypertension in Man, Bull. Johns Hopkins Hosp. **65**:353 (June) 1939. (*e*) Howard, T. L.; Forbes, R. P., and Lipscomb, W. R.: Aneurysm of the Left Renal Artery in a Child Five Years Old with Persistent Hypertension, J. Urol. **44**:808 (Dec.) 1940. (*f*) Saphir, O., and Ballinger, J.: Hypertension (Goldblatt) and Unilateral Malignant Nephrosclerosis, Arch. Int. Med. **66**:541 (Sept.) 1940.

8. Pincoffs, M. C., and Bradley, J. E.: The Association of Adenosarcoma of the Kidney (Wilms' Tumor) with Arterial Hypertension, Tr. A. Am. Physicians **52**:320, 1937. Koons, K. M., and Ruch, M. K.: Hypertension in a Seven Year Old Girl with Wilms' Tumor Relieved by Nephrectomy, J. A. M. A. **115**:1097 (Sept. 28) 1940.

logic conditions,[6] all of which can be considered examples of unilateral renal ischemia.[8a] The return of the blood pressure to normal as a result of removal of an ischemic kidney has already been reported[9] in cases of hypertension in man in which one kidney was diseased and the other was evidently normal or not significantly diseased. In personal communications to us there have been mentioned at least 25 additional cases in which unilateral nephrectomy has resulted in the return of the blood pressure to normal for periods varying from three months to two and one-half years. In most of these cases the disease was unilateral chronic pyelonephritis, with the usual intrarenal vascular changes that accompany this condition.

In man, when the presence of disease in one kidney is established it is often difficult to determine with certainty whether the other kidney is diseased and especially whether it is the seat of arteriosclerosis or arteriolar sclerosis. All studies of the other, presumably normal kidney, including clearance tests of various kinds for renal excretory function, may give results within the limits of normal; nevertheless, the kidney may be the seat of considerable vascular disease. It is impossible, therefore, to predict with certainty the probable effect on hypertension in man of removal of one obviously diseased kidney. If the other kidney is normal, the probability is great, in the light of the experimental studies on animals and the results already obtained from unilateral nephrectomy in man, that the blood pressure will return to normal after removal of the diseased kidney. If the other kidney is known to be diseased or if its excretory function is found to be somewhat impaired, unilateral nephrectomy is not indicated as a treatment for the hypertension alone and should be practiced only if it is considered advisable for the renal disease itself. This conclusion is in agreement with the views of others who have recently reviewed this subject.[10] Excision of the more diseased of two diseased kidneys for the sole purpose of possibly alleviating the hypertension is certainly not justifiable.[6g]

The results of the following experiments are of interest in connection with the general problem of the pathogenesis of hypertension due to renal ischemia and may also prove of value in solving the clinical problem whether or not to perform unilateral nephrectomy for the purpose of lowering the blood pressure in some cases of hypertension in man in which one kidney is obviously diseased and probably ischemic.

8a. Since this paper was submitted for publication, an exhaustive review, with complete bibliography, on the subject of human hypertension associated with unilateral renal disease has been published by B. S. Abeshouse (Surgery **9**:942 [June] 1941; **10**:147 [July] 1941).

9. Footnote 6. Footnote 7 *b*, *c* and *e*.

10. Footnote 6 *g*, *h*, *i* and *l*.

EXPERIMENTS

Effect on the Blood Pressure of Dogs of Unilateral Constriction of the Main Renal Artery.—On the basis of considerable experience, it has become justifiable to expect significant elevation of the blood pressure in most dogs as a result of

TABLE 1.—*Effect of Constriction of One Main Renal Artery on the Blood Pressure of the Dog*

	Preoperative Period					Postoperative Period				
	Average Weekly Blood Pressure, Mm. Hg				Maximum on Any Day	Average Weekly Blood Pressure, Mm. Hg				Maximum on Any Day
Dog	1st	2d	3d	4th		1st	2d	3d	4th	
247	120	125	120	120	140	130	135	150	152	160
248	130	125	130	120	130	127	150	138	148	155
250	147	135	141	145	150	156	180	182	175	185
253	150	145	145	140	160	171	190	175	150	190
267	143	134	137	135	150	161	190	206	201	215
268	168	166	162	160	175	180	223	226	245	250
305	155	150	145	150	160	171	188	190	200	215
306	135	135	140	130	155	165	164	150	162	195
307	145	130	147	136	170	154	164	182	180	200
313	142	148	154	152	160	183	183	175	170	210
319	125	135	130	123	140	148	160	165	160	165
326	155	155	140	152	160	161	177	165	165	190
333	135	120	120	130	140	155	172	175	170	180
335	130	135	132	132	145	164	172	175	158	185
336	130	125	137	123	135	134	130	138	135	150
339	130	125	123	125	130	147	160	160	160	165
340	150	140	145	130	150	140	152	147	145	160
342	140	135	135	137	140	178	170	172	173	200
377	145	145	150	140	150	156	168	148	148	170
384	150	125	125	133	150	158	168	165	160	175
417	145	140	145	140	145	151	170	165	160	170
428	145	140	145	140	160	148	154	135	150	165
433	110	110	108	114	120	143	150	145	160	160
434	130	125	135	130	145	148	174	186	195	200
461	130	130	135	130	135	140	155	155	148	170
505	145	130	140	130	160	174	168	155	170	185
507	160	160	150	145	160	168	198	183	180	215
532	125	120	125	122	145	154	160	150	148	165
538	145	143	145	135	155	152	168	173	168	180
539	130	125	130	135	140	144	147	133	130	155
549	145	143	143	138	150	155	164	162	160	170
590	125	125	130	128	135	137	138	130	130	145
640	115	120	120	110	120	129	152	150	143	170
646	115	110	112	118	120	137	148	145	140	155
679	135	137	130	125	140	136	157	152	148	160
680	118	112	110	103	130	129	128	122	125	145
686	140	125	130	127	140	120	129	130	120	135
701	115	115	115	110	115	127	135	133	133	135
702	125	115	110	115	125	136	130	130	127	140
739	110	105	115	112	120	138	127	121	132	145
Aver. values.	136	132	133	131	144	150	161	159	158	175

adequate constriction of the main artery of only one kidney. Inadequate or excessive constriction of only one main renal artery may fail to cause significant elevation of blood pressure or may cause slight elevation which persists for only a few days. Adequate constriction almost invariably results in a significant but variable elevation of the blood pressure. Table 1 gives the average weekly values for the direct femoral blood pressure of 40 dogs during a preoperative period of four weeks and during an equal period after constriction of one main renal artery. The maximum pressures for the two periods are also given. In these dogs, after the control period the main artery of one kidney was constricted to a variable degree by means

of a silver clamp by the method previously described.[11] All operations were performed with the dogs under ether anesthesia after the previous injection of morphine and atropine. The direct mean blood pressure was determined by the insertion (through skin and fascia) into the femoral artery of a 21 gage needle connected by a liquid system (2 per cent sodium citrate) with a mercury manometer. The data in table 1 show that in 40 dogs, almost without exception, there was a statistically significant elevation of the average direct femoral blood pressure during all of the first four weeks after constriction of the main artery of only one kidney. In some of the dogs the elevation was great; in others it was only slight. It is evident from this chart, even without special statistical analysis, that in the dog, at least, a significant but variable rise of blood pressure almost invariably results from adequate constriction of only one main renal artery.

Effect on the Blood Pressure of the Dog of Occlusion of the Ureter of One Kidney.—In 6 dogs the ureter of one kidney was occluded. The surgical incision and retroperitoneal approach were the same as for the application of a clamp on the main renal artery for the production of renal ischemia.[11] The ureter was isolated for a short distance, tied by means of four ligatures and cut so that two ligatures were left on each end. To insure permanent occlusion of both ends, the two ligatures on each cut end were then tied together.

There was no significant elevation of blood pressure at any time in any of the animals as a result of this procedure.

Effect on the Blood Pressure of the Dog of Unilateral Constriction of the Main Artery and Occlusion of the Ureter of the Same Kidney.—The purpose of this study was to determine whether unilateral renal ischemia of the degree that practically always results in elevation of blood pressure (table 1) would be effective if at the same time the excretory function of the ischemic kidney were completely arrested by occlusion of the ureter, which alone does not result in elevation of the blood pressure.

In 20 dogs, after a control period of four weeks a clamp was applied to the main artery of one kidney and the vessel constricted to a degree that is practically always (table 1) followed by some elevation of blood pressure. At the same time the ureter of this kidney was ligated and transected in the manner previously described. Table 2 shows that in 19 of these animals there was no significant elevation of blood pressure after the operation. In these animals, neither the average pressure for all of the four weeks after the operation nor the maximum pressure during any day of this period showed a significant change from the preoperative control values. Only 1 animal, dog 5-74 (table 2), showed any elevation of blood pressure during the postoperative period, and in this dog a ureteral fistula developed which lasted for about three weeks after the operation. When the fistula closed (spontaneously), the blood pressure promptly fell to normal. The first part of chart 2 (dog 5-86) is a typical illustration of the effect of constriction of the main artery and occlusion of the ureter of one and the same kidney.

Comment.—These results are in striking contrast to the effect on the blood pressure of unilateral renal ischemia due to constriction of one main renal artery alone, without interference with the ureter (table 1), and they show that in the dog ischemia in a kidney which is nonfunctioning

11. Goldblatt (footnotes 1 and 2 *c*).

so far as excretion of urine is concerned does not produce elevation of blood pressure. The failure of the blood pressure to rise, especially during the first two weeks after constriction of one main renal artery and coincident occlusion of the ureter, at a time when there is still a considerable amount of renal parenchyma, is the significant result. The absence of any effect on the blood pressure later, at a time when the renal parenchyma is in great part destroyed by hydronephrosis, is not surprising. Whether it means that the chemical substance of renal origin [12] which probably determines hypertension due to renal ischemia is not or cannot be formed in such a kidney, that it is formed in a quantity inade-

TABLE 2.—*Effect of Constriction of One Main Renal Artery and Occlusion of the Ureter of the Same Kidney on the Blood Pressure of the Dog*

	Preoperative Period					Postoperative Period				
	Average Weekly Blood Pressure, Mm. Hg				Maximum on Any Day	Average Weekly Blood Pressure, Mm. Hg				Maximum on Any Day
Dog	1st	2d	3d	4th		1st	2d	3d	4th	
404	140	138	138	138	140	127	128	122	127	140
491	131	117	121	126	140	127	132	135	120	140
493	123	117	115	117	130	126	115	120	122	130
530	127	125	135	142	145	135	132	122	122	145
537	121	120	108	120	125	125	125	125	110	135
540	134	134	133	135	145	144	140	136	135	155
553	140	126	120	128	150	123	124	126	125	140
563	123	125	123	123	130	123	122	125	123	130
574	110	120	115	116	120	140	124	130	120	145
584	126	122	125	128	135	128	125	122	120	135
586	126	125	138	128	140	131	126	122	123	135
587	145	135	145	143	150	131	125	128	128	135
588	155	150	155	157	160	154	146	140	140	160
596	140	140	134	143	150	137	133	132	133	145
599	135	133	128	130	140	125	125	118	119	135
600	145	141	132	130	145	134	144	135	135	145
623	125	125	120	130	150	127	125	128	115	135
645	135	125	120	130	135	133	131	120	115	155
665	125	125	125	128	135	125	127	123	120	135
708	120	115	120	118	125	119	118	118	112	125
Aver. values.	131	128	128	131	140	131	128	126	123	140

quate to be effective in the presence of one normal kidney or that it is formed in the same quantity as in any ischemic kidney but does not enter the blood stream in a substantial quantity in a given time, on account of the greatly reduced outflow of blood from the kidney, is answered, at least in part, by the following experiments.

Effect on Blood Pressure of Occlusion of the Ureter of the Ischemic Kidney in a Dog with Hypertension Due to Unilateral Constriction of the Main Renal Artery.—In 4 dogs with definitely elevated blood pressure resulting from constriction of the main artery of one kidney the ureter of this kidney was ligated and transected. As a result, there was a fall of the blood pressure to normal. Occlusion of the ureter was carried out at a time when a natural return of the blood pressure

12. Goldblatt.[2] Fasciolo and others.[3f]

to normal was not expected, and the drop of the blood pressure to normal, although it took from three to seven days, was more rapid than is usual in an animal with unilateral renal ischemia. The fact that the fall to normal required several days indicates that the substance from the ischemic kidney which brings about the pressor effect continued to enter the circulation in sufficient quantity at least for several days after the ureter was occluded. Chart 1 (dog 7-78) is illustrative of all 4 experiments. The effect of occlusion of the ureter on the blood pressure can be interpreted as due either to gradual interference with the entrance of the pressor-producing substance into the circulation or to a gradual cessation of its formation as the hydronephrosis developed.

Effect on the Blood Pressure of Dogs of Constriction of the Main Arteries and Occlusion of the Ureters of Both Kidneys.—In 3 dogs the main artery of one kidney was moderately constricted and the ureter of the same kidney occluded in the same operation. As soon as it was certain that this had failed to affect the blood pressure, the same procedures were carried out on the other kidney. The invariable result

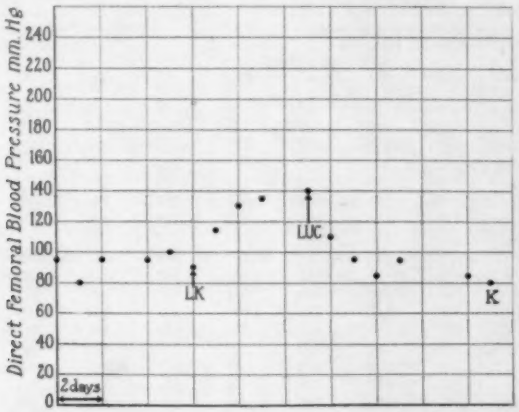

Chart 1 (dog 7-78).—Effect on blood pressure of occlusion of the ureter after the blood pressure has become elevated owing to constriction of the main artery of one kidney. *LK*, moderate constriction of the left main renal artery. *LUC*, occlusion by ligation and transection of the left ureter. *K*, killed.

was uremia, as in the case of excessive constriction or occlusion of both main renal arteries [13] or occlusion of both ureters, and this was accompanied, as in the conditions just mentioned, by slight to moderate elevation of blood pressure. The animals with uremia and considerable hypertension developed the typical arteriolar lesions of the malignant phase of experimental hypertension due to excessive renal ischemia, previously described.[14] Chart 2 (dog 5-86) is illustrative of the 3 experi-

13. Footnotes 1 and 2.

14. Goldblatt, H.: Studies on Experimental Hypertension: VII. The Production of the Malignant Phase of Hypertension, J. Exper. Med. **67**:809 (May) 1938; Studies on Experimental Hypertension: XIII. Experimental Observations on the Malignant Phase of Essential Hypertension; the Production of Intrarenal

(Footnote continued on next page)

ments. Thus, in animals with both kidneys ischemic owing to constriction of the main arteries and with the ureters occluded as well the result was not like that of bilateral nephrectomy, which does not produce elevation of blood pressure,[2b] but more like that of excessive constriction of one main renal artery with occlusion of the ureter of the other kidney.[14] The absence of the inhibitory, neutralizing or compensating effect of a normal kidney [15] evidently resulted in elevation of the blood pressure due to entrance into the circulation of an otherwise inadequate amount of pressor-producing substance.

Effect on the Blood Pressure of the Dog of Constriction of the Main Artery and Occlusion of the Ureter of One Kidney, with Contralateral Nephrectomy.—In 3 dogs the main artery of one kidney was moderately constricted and the ureter tied and cut as has been described. After four to six days, during which time there was no significant rise of blood pressure and before much destruction of renal parenchyma

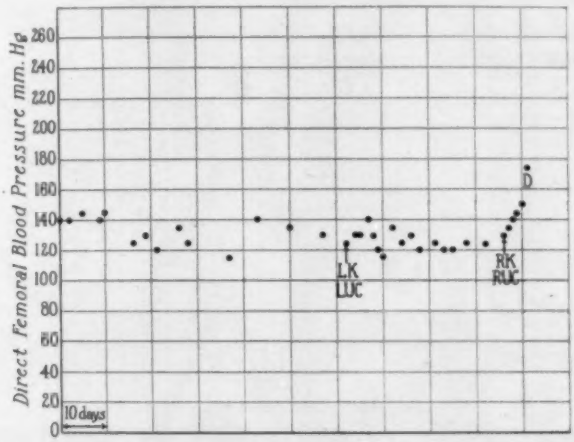

Chart 2 (dog 5-86).—Effect on blood pressure of constriction of both main renal arteries and occlusion of both ureters. *LK*, moderate constriction of the left main artery. *LUC*, occlusion of left ureter. *RK*, constriction of right main renal artery. *RUC*, occlusion of right ureter. *D*, died.

by hydronephrosis could occur, the other kidney was excised. In both animals there was then a moderate but significant elevation of the direct femoral blood pressure, which was evident about twenty-four hours after nephrectomy and persisted until the animal died, in uremia. Chart 3 (dog 6-22) illustrates this result, which is like that obtained from excessive constriction or occlusion of one

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and Extrarenal Arteriolar Necrosis and Necrotizing Arteriolitis, in Blood, Heart and Circulation, Publication 13, American Association for the Advancement of Science, New York, Science Press Printing Company, 1940, p. 266.

15. Rodbard, S., and Katz, L. N.: The Rôle of Renal Metabolism in Hypertension and Uremia, J. Exper. Med. **73**:357 (March) 1941. Goldblatt and others.[1a] Goldblatt.[2c] Katz and others.[3b]

main renal artery with contralateral nephrectomy, and can be attributed to the absence of the compensating, neutralizing or inhibiting effect of a normal kidney.[15]

Comment.—On the basis of the preceding two series of experiments it can be stated that the failure of the blood pressure to become elevated in a dog with the main artery of one kidney constricted and the ureter of the same kidney occluded and with a contralateral normal kidney is not due to the absence of a pressor-producing substance from the venous blood of such a kidney. Direct evidence that a vasoconstrictor substance is actually present in the venous blood from the ischemic kidney with the ureter occluded and not in the venous blood from the normal kidney is supplied by the following experiments.

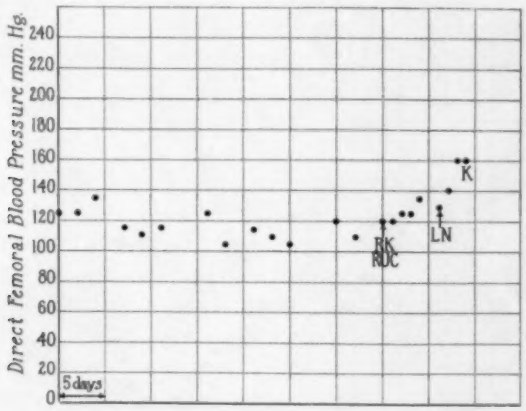

Chart 3 (dog 6-22).—Effect on blood pressure of constriction of the main artery and occlusion of ureter of one kidney followed by excision of the contralateral normal kidney. *RK*, moderate constriction of the right main renal artery. *RUC*, occlusion of the right artery. *LN*, left nephrectomy. *K*, killed.

Vasoconstrictor Property of Venous Blood Plasma from a Kidney with the Main Artery Constricted and the Ureter Occluded, Compared with Venous Blood Plasma from the Contralateral Normal Kidney and with Systemic Venous Blood Plasma.—In 9 dogs with the main renal artery constricted and the ureter occluded in which no rise of blood pressure had occurred in from five to ten days after the operation, the main vein of each kidney was cannulated and blood obtained for a test (Läwen-Trendelenburg technic) for vasoconstrictor substance in the citrated plasma. At the same time an additional control specimen of blood from the jugular vein was obtained for the test. The blood was obtained while the animal was under pentobarbital sodium anesthesia. The technic of the test was that described by Fasciolo, Houssay and Taquini.[af] The same final dilution of blood plasma in sodium citrate and Ringer's solution was employed. Bufo peltacephalus, a giant toad from Cuba, was used for the tests. The hind portion of the toad was first perfused through the abdominal aorta with 0.5 per cent sodium citrate in Ringer

solution from a Marriott bottle, and the outflow of drops from the abdominal vein was counted at intervals of five minutes until the rate of flow was constant. Then the fluid was changed abruptly to the citrated plasma to be tested, and the perfusion was continued for twenty-five minutes. Counts of the outflow were made at intervals of five minutes. The difference between the number of drops at the point of greatest change of flow and the number of drops at the constant level, expressed in per cent of the constant value, was regarded as the index of constriction or dilatation of the peripheral vessels in the perfused portion of the toad. Two 25 cc. samples of venous blood (for two separate tests) were usually obtained from each kidney, and as a rule only one sample of systemic blood was assayed. The plasma, diluted, 1 part in 7 parts of 0.5 per cent sodium citrate solution in Ringer's solution without calcium, was the final fluid tested. The rate of outflow of blood from the renal vein of the ischemic kidney was almost always slower than from the normal,

TABLE 3.—*Results of Comparative Tests*

Dog	Number of Days After Operation Samples of Venous Bloods Were Obtained	Degree of Constriction or Dilatation Produced by Plasma From Venous Blood of Ischemic Kidney with Ureter Occluded	From Venous Blood of Normal Kidney	From Systemic Venous Blood
8-24	8	—83	— 7	+58
8-11*	6	—35 (left kidney) —80 (right kidney)	....	— 8
8-08	7	—50	+15	+41
8-09	7	—46	+40	+22
8-10	7	—32	—13	+10
8-26	7	—23	— 1	+72
8-07	6	— 7	0	+10
8-05	7	+ 7	+22	+70
8-06	4	+56	+136	+87

* In this animal the left main renal artery was first constricted and the left ureter cut. Two weeks later the same operations were performed on the right side. Both kidneys were therefore ischemic.

but the difference between the two rates varied, depending on the degree of constriction of the main renal artery.

The tests were all carried out objectively; the investigator who performed them did not know the source of the various specimens until the result was obtained. In table 3, which gives the results of the tests, the minus sign before the values indicates constriction and the plus sign dilatation. Although the degree of constriction effected by the venous blood from the kidneys with the renal artery constricted and the ureter occluded varied greatly, there was a significantly constrictive effect from the plasma of at least 6 of the 9 animals. On the contrary, the plasma from only one normal kidney produced some constriction, while that from the remainder showed no effect or a variable degree of dilatation. There was almost always a definite, though variable, dilator effect from the systemic venous blood plasma, although the latter has a greater viscosity than the control Ringer solution. In the case of dog 8-06 (table 3), the result was strikingly different from all others and may have been due to some undetected technical irregularity in the preparation of the toad, to some error in the preparation of the Ringer or the citrate solution or to inadequate constriction of the renal artery. A few experiments were performed which showed that the vasoconstrictor effect was not due to

epinephrine or tyramine, and the fact that the vasoconstrictor effect was not reversed by piperidomethyl-3-benzodioxane (933 F) indicates that the vasoconstrictor substance in the plasma was probably identical with that which has been found in the venous blood from kidneys with the main artery constricted and the ureter intact [3f] and which is now regarded as the humoral agent that produces renal hypertension.[16]

GENERAL COMMENT

This study is reported at this time because of the possible practical application of the results already obtained to the problem of the performance of unilateral nephrectomy for the treatment of hypertension in man when it is associated with unilateral renal disease. It is justifiable to suggest that if in cases of such association there is no output of urine from the diseased kidney, owing to occlusion of the ureter from any cause, the probability is great that the hypertension is due either to disease of the other kidney or to some other cause. Lowering of the blood pressure should not be expected, therefore, to result from excision of a completely nonfunctioning kidney whose lack of function is due to occlusion of the ureter, even though there is some indication that in man such a kidney may still be the source of a hypertensive effect. In such circumstances, for the present at least, nephrectomy is perhaps best performed only if the obviously diseased kidney is the source of other untoward clinical effects (infection or persistent pain, for example) for which removal of the kidney might in any event be indicated.

Several cases of unilateral nephrectomy for complete hydronephrosis in which a return of the elevated blood pressure to normal has occurred and has persisted for several months after the operation have been reported to us. In 1 of these cases the kidney showed such advanced destruction, with practically no tubules and only relatively few glomeruli left in the wall of the sac, that it is difficult to accept this as the source of the hypertensive effect. Yet for several months after the nephrectomy the blood pressure remained normal. At the Cleveland City Hospital, in the service of Dr. R. W. Scott, there was observed a case of unilateral chronic pyelonephritis, with the usual intrarenal vascular disease, in which before the operation no urine was obtained from the affected kidney and no indigo carmine was excreted by it, although the pelvis could be filled from below. The patient's systolic blood pressure was usually 200 mm. of mercury or more, and the diastolic 120 mm. or more, before the operation; yet within a day after the operation the blood pressure fell to 120 systolic and 80 diastolic, and it has remained within

16. Page, I. H.: Newer Aspects of Experimental Hypertension, in Blood, Heart and Circulation, Publication 13, American Association for the Advancement of Science, New York, Science Press Printing Company, 1940, p. 239. Blalock, A.: Experimental Hypertension, Physiol. Rev. **20**:159 (April) 1940.

normal limits during a period of five weeks since the operation. On the day of the patient's discharge from the hospital the blood pressure was 108 systolic and 78 diastolic.

SUMMARY AND CONCLUSIONS

Constriction of one main renal artery in the dog causes a variable rise of blood pressure, which persists for a variable period. Excision of the ischemic kidney results in a prompt fall of the blood pressure to normal. Similarly, in man, hypertension may be associated with unilateral renal disease, presumably producing ischemia, and removal of the diseased kidney results in a fall of the blood pressure to normal if the other kidney is normal.

Occlusion of one ureter in the dog does not result in elevation of blood pressure. Occlusion of the ureter performed at the same time that the main artery of the same kidney is constricted interferes with the development of the elevated blood pressure of a dog with unilateral renal ischemia. After the blood pressure has become elevated owing to constriction of one main renal artery, occlusion of the ureter of the same kidney causes a fall of blood pressure to normal in from three to seven days. Constriction of both main renal arteries accompanied with occlusion of both ureters usually results in a moderate elevation of blood pressure, which persists until death of the animal in uremia. Occlusion of the ureter and constriction of the main artery of one kidney followed by contralateral nephrectomy also usually results in a moderate elevation of blood pressure, which persists until death occurs in uremia. A hypertensive effect is, therefore, produced by kidneys with the main artery constricted and the ureter occluded when no normal kidney is present.

A vasoconstrictor effect has been obtained (by the Läwen-Trendelenburg technic) with citrated plasma of the venous blood of kidneys with the renal artery constricted and the ureter occluded, although the blood pressure of the animals was not elevated. No vasoconstrictor effect, but rather a dilator effect, was obtained with the plasma of venous blood from the contralateral, normal kidney and of systemic venous blood. This indicates that the effect of occlusion of the ureter on a kidney with the main artery constricted is not to abolish the production of pressor substance but to interfere with the rate of entrance of pressor-producing substance from the kidney into the systemic circulation or diminish the amount produced. In either case, the failure of the blood pressure to become elevated as a result of the decreased amount of pressor-producing substance which enters the systemic circulation may also be due to the neutralizing effect of the contralateral normal kidney.

Although some human beings have already been described in whom excision of a kidney with the ureter completely obstructed or of a kidney from which no urine was obtained was followed by a return of the blood pressure to normal, the experiments indicate that this may not prove to be the rule and that in such cases excision of the kidney should be undertaken for the main purpose of removing the diseased organ rather than for possible cure of the hypertension. In all cases of contemplated unilateral nephrectomy it is desirable, with the limited means available at present, to determine that the other kidney is, as far as can be determined, normal, before removing an obviously diseased, though still functioning, kidney for the possible favorable effect of this procedure on the elevated blood pressure.

NAEVUS UNIUS LATERIS

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One of the most interesting and certainly the most unusual of the varieties of nevi is the so-called neuropathic papilloma, or naevus unius lateris. It is a papillary or verrucous congenital tumor having a unilateral or nearly unilateral distribution in linear streaks or bands following the long axis of the limbs or extending transversely around the trunk. This unique disease is so striking that it is readily recognized as a distinct clinicopathologic entity. Only 4 cases have been observed among 40,000 patients with tumors studied at the Memorial Hospital, an incidence of 0.01 per cent. To these have been added 156 cases from the literature, thus affording 160 cases for analysis.

SYNONYMS

The term naevus unius lateris was originated by von Baerensprung in 1863. Theories as to etiology, variations in appearance of the reported lesions and attempts to create names embodying both descriptive and pathogenetic elements have led to the appearance of a host of synonyms in the literature, of which the following are examples: naevus linearis unius lateralis, naevus verrucosus unius lateris, linear nevus, systematized nevus, naevus unilateralis, naevus lateralis, naevus verrucosus, naevus papillaris, naevus pigmentosus unius lateris, naevus nervosus, naevus papillaris neurosus, *naevus verruqueux unilateral, naevus verruqueux zoniformis, naevus lichenöide, naevus lichenöide kératopilaire, naevus kératosique systématisé,* naevus neuroticus, naevus linearis verrucosus, naevus linearis ichthyosiformis, naevus neurapathicus, verrucopapillomatosis, ichthyosis hystrix congenita, ichthyosis cornea, ichthyosis cornea (hystrix) partialis, ichthyosis linearis neuropathica, ichthyosis hystrix nigricans, ichthyosis linearis congenitalis, papilloma neuropathicum,

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papilloma neuroticum, *papilloma corné neurotique,* papilloma essentiale neuropathicum, papilloma neuropathicum unilaterale, unilateral papilloma, *papillome eczématiformé;* eczema neuroticum, *keratose linéaire systématisée,* neurodermitis linearis chronica verrucosa, congenital neuropathic warts and congenital papillary streaks.

CRITERIA

Von Baerensprung [1] stated that this nevus is always unilateral and limited to the median line; that the areas affected correspond to the peripheral distribution of one or more nerves; that the subcutaneous changes consist in hypertrophy of the papillae—in which the nerves terminate—and that glands and hairs take no part in the development of the lesion.

Morrow [2] concluded that the expression "linear naevus" is adequate. He stated the belief that all the lesions present certain objective characteristics sufficiently similar to justify their inclusion in the same category. The more typical of these characteristics are:

1. There is linear distribution, following the long axis of the limb or directed transversely on the trunk.
2. The distribution is unilateral.
3. The nevus is papillary or verrucous.
4. The origin is congenital, the nevus commonly appearing at birth or in the first few months of life but occasionally during adolescence or later.
5. Sensory disturbances are often a marked feature but may be entirely absent.
6. The nevus may increase in extent, remain stationary, spontaneously retrogress or undergo various degenerative changes (exceptionally malignant transformation).

Heidingsfeld [3] agreed with Morrow's criteria and expressed the belief that three or four of these characteristics are enough for diagnosis. Adamson,[4] however, stated the opinion that the verrucous type of nevus is not the only form and that the growth may involve any element of the

1. von Baerensprung: Naevus unius lateris, Charité-Ann. **11**:91, 1863.
2. Morrow, P. A.: Two Cases of Linear Naevus, with Remarks on Its Nature and Nomenclature, New York M. J. **67**:1, 1898.
3. Heidingsfeld, M. L.: Linear Naevi, J. A. M. A. **43**:597 (Aug. 27) 1904.
4. Adamson, H. G.: Some Remarks on Zoniform or Segmented Naevi, Brit. J. Dermat. **26**:379, 1914.

skin, a point which Étienne [5] had previously made. Meissner [6] pointed out three characteristics common to this type of nevus:

1. Congenital origin, the lesion appearing at birth, early in childhood, during pregnancy or in the puerperium.
2. Failure to pass the midline.
3. Absence of deleterious effect on vital processes or general health.

ETIOLOGY

Many theories as to the cause of this nevus have been conceived, and objections have been made to all of them. Von Baerensprung [1] expressed the belief that the site of the disease is in the spinal ganglions and that the distribution of the nevi coincides with the extension of the cutaneous nerves. This theory, or modifications of it, has had many adherents. Hyde,[7] Mackenzie,[8] Kudisch [9] and Plonski [10] agreed that intrauterine disease of the spinal ganglions causing persistent trophic disturbance is the probable cause. Gerhardt [11] concluded that the nevus is the result of disease affecting the central nervous system, a view later shared by Reckzeh [12] and Lewith.[13] Müller [14] concluded that the lesions correspond more to central than to peripheral nerves. Spietschka [15] saw significance in the fact that in some cases the patients showed nervous disturbances. Hagen [16] expressed the belief that congenital diseases of the skin with

5. Étienne, G.: Naevi dans leurs rapports avec les territoires nerveux; essai de pathogénie et d'etiologie, Nouv. iconog. de la Salpêtrière **10**:263, 1897; abstracted, Brit. J. Dermat. **10**:28, 1898.

6. Meissner, P.: Ueber Naevus verrucosus, Dermat. Ztschr. **2**:478, 1894-1895; abstracted, Brit. J. Dermat. **8**:407, 1896.

7. Hyde, J. N.: Rare Form of Congenital, Multiple and Monolateral Pigmentary Naevus, Having the Disposition of Zoster Corporis, Chicago M. J. & Examiner **35**:377, 1877.

8. Mackenzie, S.: Papillary Growths of Nervous Distribution, M. Times & Gaz. **1**:451, 1880.

9. Kudisch: Naevus Pigmentosus unius lateris, Monatsh. f. prakt. Dermat. **50**:173, 1910.

10. Plonski: Ueber Naevus verrucosus, Dermat. Ztschr. **10**:390, 1903.

11. Gerhardt, C.: Beobachtungen über neuropathisches Hautpapillom, Jahrb. f. Kinderh. **4**:270, 1871.

12. Reckzeh: Naevus verrucosus pigmentosus unius lateris, Med. Welt **8**:1406, 1934.

13. Lewith, R.: Ueber systematisierte Naevi und "naevusartige" Dermatosen, Arch. f. Dermat. u. Syph. **169**:582, 1934.

14. Müller, J.: Ein Fall von Naevus verrucosus unius lateris, Arch. f. Dermat. u. Syph. **24**:21, 1892.

15. Spietschka, T.: Ueber sogenannte Nerven-Naevi, Arch. f. Dermat. u. Syph. **27**:27, 1894.

16. Hagen, A.: Zur Kenntnis des halbseitigen Naevus verrucosus, Münchn. med. Wchnschr. **39**:329, 1892.

disturbances of the central nervous system are due to deep-lying abnormal processes causing both. Nicolas, Rousset and Colas [17] concluded that the coincidence of cutaneous lesions and skeletal malformations is in favor of the neural theory. Lewin,[18] however, in reviewing 100 cases of this type of nevus found that in only 40 cases was the correspondence of the lesions to nerve distribution sufficient to suggest a neural influence.

Because of this discrepancy in many cases, Philippson [19] explained the distribution of systematized nevi as determined by the lines of Voigt, i. e., the boundaries of the areas of distribution of the main cutaneous nerve stems. This theory was also brought forth by Hallopeau.[20]

Blaschko [21] assumed disturbed development of the epidermis in the embryo at the margin of a segment of skin, which might later involve the entire segment by surface extension of cornified epithelial ridges running in the same directions as cleavage lines of the skin and hair streams and that later in life the lines of the nevus might be influenced by irregular growth or by body movements. Jadassohn [22] expressed agreement with direction of hair streams. Okamura [23] agreed with Blaschko and Jadassohn concerning hair streams and concluded that the lesion is caused by hypertrophy of the ectoderm due to changes in the mesoderm.

Kopp [24] connected the configuration of nevi with vascular distribution. Heller [25] is cited as the first to consider the dependence of systematized nevi on the lymphatic system, and Meissner [6] expressed the belief that

17. Nicolas, J.; Rousset, J., and Colas, J.: Naevi verruqueux hyperkératosiques systématises zoniformes à disposition unilatérales, Bull. Soc. franç. de dermat. et syph. **43**:819, 1936.

18. Lewin, in discussion on Meissner: Ueber Naevus verrucosus unius lateris, Arch. f. Dermat. u. Syph. **33**:204, 1895.

19. Philippson, L.: Zwei Fälle von Ichthyosis cornea (hystrix) partialis (Naevus linearis verrucosus, Unna), entsprechend dem Verlaufe der Grenzlinien von Voigt, Monatsh. f. prakt. Dermat. **11**:337, 1890.

20. Hallopeau, cited by Bohac.[31]

21. Blaschko, A.: Bemerkungen zu vorstehenden Aufsatz (Alexander), Dermat. Ztschr. **2**:361, 1895.

22. Jadassohn, J.: (*a*) Beiträge zur Kenntnis der Naevi, Vrtljschr. f. Dermat. u. Syph. **15**:917, 1888; (*b*) Zur Kenntnis der systematisierten Naevi: II. Bemerkungen zur Histologie der systematisierten Naevi und über "Talgdrüsen-Naevi," ibid. **33**:355, 1895; (c) III. Zur Lokalization der systematisierten Naevi, ibid. **33**: 373, 1895.

23. Okamura, T.: Zur Kenntnis der "systematisierten Naevi" und ihres Ursprungs, Arch. f. Dermat. u. Syph. **56**:351, 1901.

24. Kopp, C.: Zur Kasuistik des Naevus vasculosus verrucosus faciei (Darier), Deutsches Arch. f. klin. Med. **84**:135, 1905.

25. Heller, cited by Schmidt, O.: Betrachtungen über einen ungewöhnlich ausgebreiteten und morphologisch heterogenen Fall von systematisiertem Gewebsnaevus, Inaug. Dissert., Göttingen, 1934.

warty nevi may be secondary to lymphangiectasis. This theory was viewed favorably by Adamson.[4] Virchow [26] stated that vascular nevi occur in certain linear arrangements due to disturbance of closing of fissures in fetal life, a view which was later taken by Hasselmann [27] in regard to verrucous nevi.

Lindenheim [28] expressed the belief that there is a definite metameral relation to the distribution of nevi. Konzert [29] attributed nevi to segmental change in embryonic life, with the change in the central nervous system due to involvement of the ectoderm. It was the conclusion of Batut [30] and Bohac [31] that the lesions can be explained on the basis of ectodermal changes without bringing nerves into consideration.

Montgomery [32] in 1901 discussed the most prominent theories: 1. The lines follow the course of cutaneous nerves. 2. The lines run along Voigt's lines. 3. The lines follow lines of cleavage of the skin. 4. The lines follow the course of blood vessels. 5. The lines run in metameres or segments of the body. 6. The lines lie along embryonic sutures and follow the trend of growth of the tissues. He stated that the first theory is inadequate because the lesions often do not follow the same nerve throughout their extent. Similarly, as to the second theory, they often cross Voigt's lines. There are likewise many exceptions to the third theory, and the fourth was never long entertained. The fifth does not explain the lesions running up and down the back in the median line. Montgomery stated that the last theory most nearly fills all requirements. The nevus originates at an early stage of development of the fetus, when embryonic layers are still a plastic mass. The disturbing agent, whatever its nature, usually affects what will later become the papillary layer of the skin and usually falls on one or the other side of the midline. Afterward, with the closing of sutures, cells may be pulled one way or the other. Groups of cells become stretched along the line and follow the twists and turns. His objections to the theory were that

26. Virchow, R., cited by Schmidt, O.: Betrachtungen über einen ungewöhnlich ausgebreitenten und morphologisch heterogenen Fall von systematisierten Gewebsnaevus, Inaug. Dissert., Göttingen, 1934.

27. Hasselmann, C. M.: Naevus Pigmentosus Verrucosus Unilateralis: The First Case in a Filipino, Jap. J. Dermat. & Urol. **35**:611, 1934; abstracted, Arch. Dermat. & Syph. **31**:398 (March) 1935.

28. Lindenheim, H.: Zur Kenntnis der systematisierten Naevi, Dermat. Ztschr. **24**:144, 1917.

29. Konzert, R.: Zur klinischen und anatomischen Kenntnis der systematisierten Naevi, Dermat. Wchnschr. **74**:1051, 1924.

30. Batut: Des naevi systematisés, J. d. mal. cutan. et syph. **16**:414, 1904.

31. Bohac, C.: Beitrag zur Kenntnis des Naevus ichthyosiformis, Dermat. Ztschr. **14**:535, 1907.

32. Montgomery, D. W.: The Cause of Streaks in Linear Naevus, J. Cutan. & Genito-Urin. Dis. **19**:455, 1901.

it premises longitudinal growth of transverse lesions; also, if streaking is due to stretching of a group of lesions, it should become attenuated, but it actually does not.

REPORT OF CASES

CASE 1.—A. V., a white American-born girl, was first seen at the Memorial Hospital on June 19, 1929, at the age of 13, because of an extensive pigmented verrucous and papillary nevus involving the left side of the body.

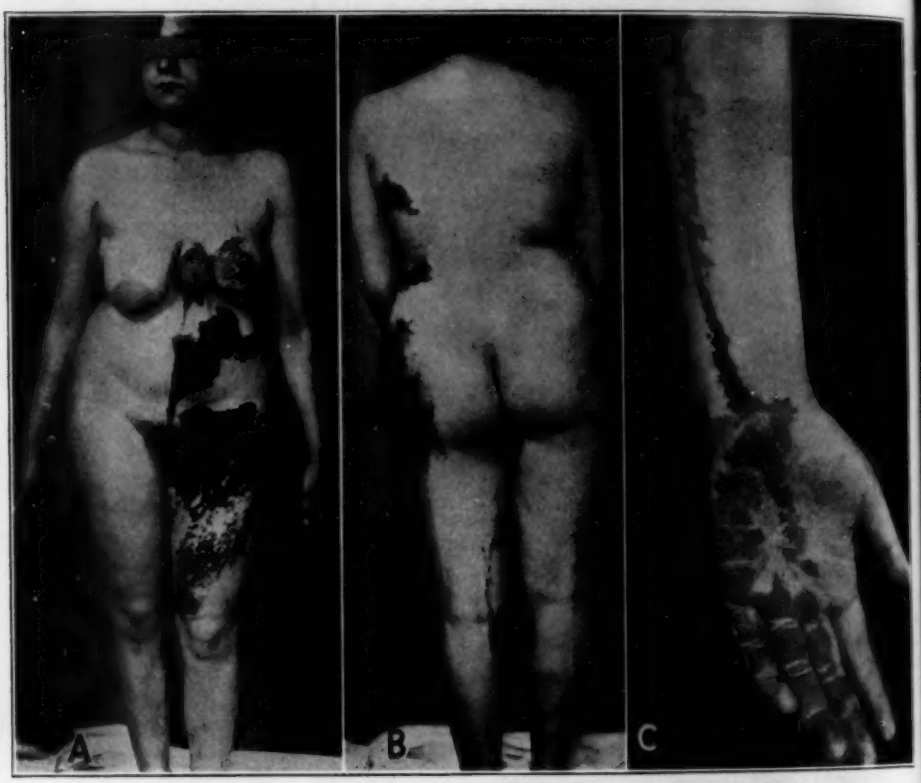

Fig. 1 (case 1).—Patient (aged 13) on June 19, 1929, before treatment. *A*, anterior view showing the distribution of the naevus unius lateris, the difference in the size of the breasts and the fungiform, papillary tumors in the umbilical and intermammary regions. *B*, posterior view, showing the distribution of the nevus on the trunk, left thigh and leg. *C*, arrangement of the nevus on the left forearm and hand.

Immediately after birth the mother noticed the lesions involving the left side of the body. She stated the belief that they were as extensive then as at the time of admission. Menstruation began at the age of 11, with normal, regular

periods. At the same time the breasts developed, but the right breast became more prominent than the left, and at the time of the girl's first appearance at the hospital it was 50 per cent larger. Three or four months before presentation a tumor mass formed between the breasts; it was painful and grew fairly rapidly.

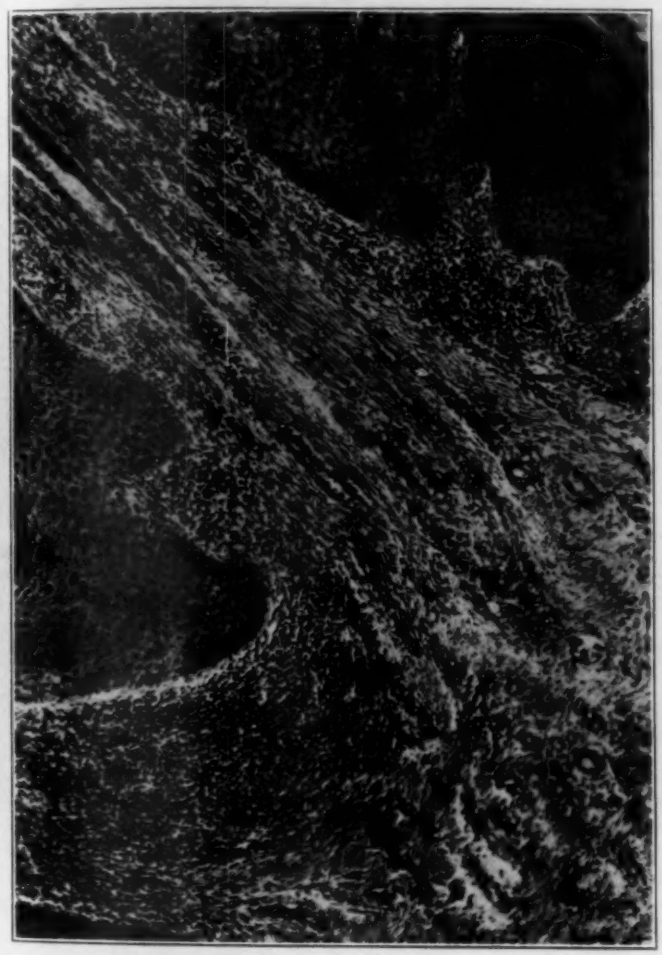

Fig. 2 (case 1).—Photomicrograph of a papillary tumor removed from the intermammary region on July 10, 1929, showing dense plasma cell infiltration of the corium. Medium power magnification.

Physical examination showed the patient to be healthy, overdeveloped and of normal mentality. She had no physical abnormalities other than the cutaneous lesion. The papillomatous, warty growth was arranged in large patches and streaks, confined entirely to the left side of the body and sharply limited by the

median line anteriorly (fig. 1). On the abdomen a line extended vertically from the xiphoid to the mons veneris but did not involve the vulva. From this line, below the umbilicus, there extended upward and to the left a roughly trapezoid solid patch. Just below the breast, a broad, densely covered band curved posteriorly from this mass over the iliac crest, with the concavity upward, and terminated just below the posterior superior iliac spine. Another closely covered patch extended from the lateral aspect of the pubis over the lower part of the abdomen, the inguinal region and the anterior and medial aspects of the upper part of the thigh. From the upper medial portion of the thigh a line of verrucous

Fig. 3 (case 1).—Photomicrograph of a naevus unius lateris removed from the back on July 11, 1930. Marked hyperkeratosis, distortion and variations in thickness of the epithelial layer can be seen, as well as elongation of the papillae. Some groups of cells suggestive of "nevus cells" are seen in the corium, but these cells as a rule are never conspicuously present in this type of nevus.

lesions extended down the posteromedial aspect of the thigh, the popliteal region and the calf, to terminate in a scattered patch on the medial aspect of the middle third of the leg. The left breast was covered by small patches and small discrete nevi with intervening areas of normal skin. The areola and the nipple were involved. From the lateral aspect of the breast a dense patch extended into the axilla and was continued posteriorly as a horizontal band which ended just lateral

to the lower angle of the scapula. On the flexor surface of the left forearm, beginning just below the elbow, a line consisting of irregular small patches of warts curved down to the anteromedial aspect of the wrist, where it spread out to extend in two irregular patches across the medial aspect of the palm, involving the entire volar aspect of the fourth and fifth fingers and the anteromedial aspect of the third finger. At the upper extremity of the vertical abdominal line, between the breasts, was a fungating, mound-shaped, papillary, cauliflower-like tumor mass measuring 10 cm. in diameter at the base and elevated about 6 cm.

Fig. 4 (case 1).—Result of multiple stage excisions (June 17, 1936). *A*, anterior view, revealing scars and skin grafts following partial excisions of the nevus. *B*, posterior view, revealing minimal scarring on the left side of the back following excisions and plastic closures.

The patient was given two low voltage roentgen ray treatments (June 24 and 27) to the mass between the breasts, and on July 10 the mass was widely excised. Microscopic examination of the specimens showed only papillary nevus with marked secondary inflammation (fig. 2). On August 7 the abdominal nevus, together with

a margin of surrounding normal skin, was excised with the endotherm knife. The area granulated well, and on September 4 Thiersch grafts and a few Reverdin grafts were applied to the abdominal wound.

On July 10, 1930, the girl was readmitted to the hospital. On the following day the two nevi on the posterolateral aspects of the chest and flank were removed by

Fig. 5 (case 1).—Photomicrograph of a nevus removed from the medial aspect of the thigh on June 18, 1936, revealing the hyperkeratotic, papillary character of the tumor. Low power magnification.

sharp dissection (fig. 3). Elliptic incisions were made and closed by primary suture. By November 10 she had three ulcerations on the left breast, which continued for two months. On Jan. 23, 1931, she was given two roentgen ray treat-

ments to the left breast, with marked improvement. Another roentgen treatment was given to the breast September 14, with subsequent improvement.

On April 5, 1932, the patient was again admitted to the hospital but refused operation and was discharged two days later. As the thigh showed late improvement in response to roentgen therapy, she was given two more treatments (July 28 and September 15). There was disappearance of numerous growths, but on November 28 there developed a radiation ulcer in the skin of the thigh, which persisted and increased to 8 cm. in diameter.

She was admitted to the hospital for the fourth time on Jan. 11, 1933, and an excision of the ulcer and the surrounding nevus was performed. On February 2, Reverdin grafts were applied. By this time the nevus had been for the most part obliterated or excised, the only remaining areas of pronounced growth being on the medial and lateral aspects of the thigh. Although further excision was urged,

Fig. 6 (case 1).—Ulcerated carcinoma of the left breast (March 20, 1939) in a patient who had a naevus unius lateris.

the patient refused until June 17, 1936, when she again entered the hospital. The result of the treatment up to this date is shown in figure 4. The following day a long patch of the tumor was excised from the medial aspect of the thigh (fig. 5). She was discharged on July 17.

After this hospitalization the patient would not return to the clinic for three years. When next seen (March 20, 1939), she complained of swelling of the left breast, with increased heat and hardening of the skin. Examination showed most of the breast to be involved by a hard ulcerated tumor mass, which had invaded the skin (fig. 6). There were large hard nodes in the left axilla. Aspiration biopsy showed mammary carcinoma. Roentgen study of the chest at that time did not show metastasis; so a wide radical mastectomy was performed on March 31. A cutaneous defect was left in the central portion of the incision and was later repaired by graft-

ing, with satisfactory healing. Microscopic study showed infiltrating mammary carcinoma grade II (fig. 7), with metastatic carcinoma in the axillary nodes. On April 10 a roentgenogram showed pulmonary metastases. The patient was discharged on April 20 and died at her home on June 9, at the age of 23.

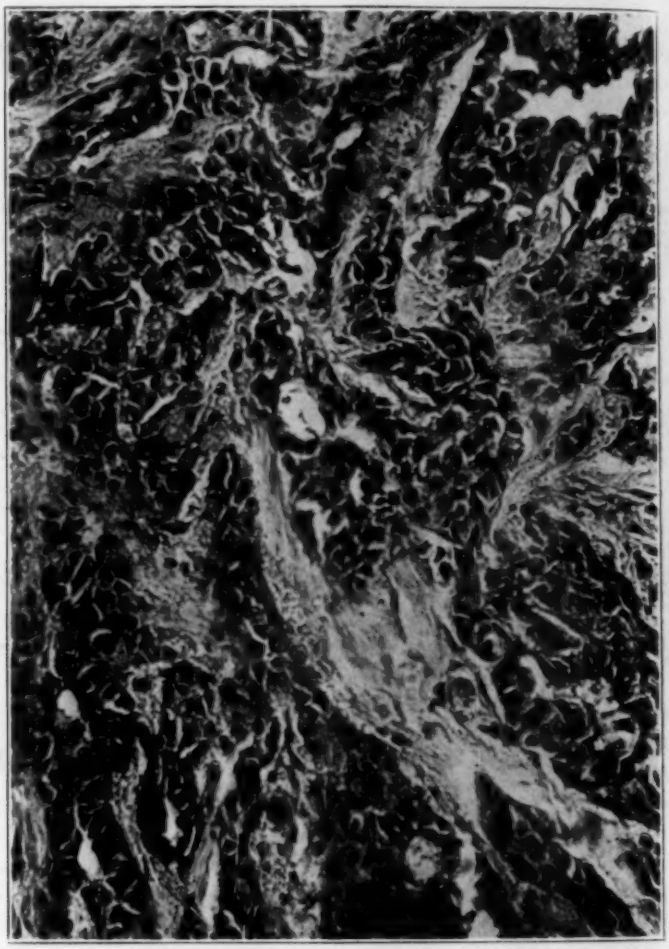

Fig. 7 (case 1).—Photomicrograph of the mammary carcinoma shown in figure 6.

Case 2.—E. L., a white, American-born 39 year old man, first presented himself at the Paterson General Hospital on Dec. 9, 1933. He had a papillary pigmented nevus distributed on the right side of the chest and the right arm.

Since birth the patient had presented a pigmented horny nevus on the skin of the right side of the chest wall and the right arm, with a few isolated lesions on the

forearm and hand. The growth had always been confined to the right side of the body and had not changed in extent. There had generally been a foul-smelling watery discharge from several regions of the nevus, and occasionally bleeding occurred when the surface was cleaned.

On his first appearance at the hospital physical examination showed an excellent general condition, there being no abnormality other than the presenting cutaneous lesion. This was a papillary, warty dark brown nevus limited to the right side of the body. The individual lesions were arranged in large plaques, broad bands and occasional smaller patches and streaks (fig. 8).

Sharply demarcated at the midline anteriorly, extending above and below the xiphoid process, was a plaque which terminated inferiorly in a finger-like projection

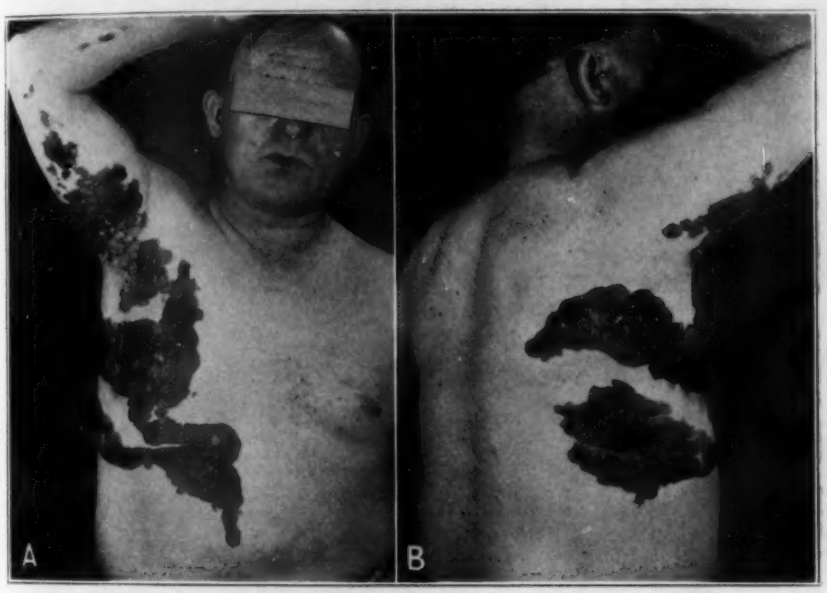

Fig. 8 (case 2).—Photographs taken Dec. 14, 1933, before treatment. *A*, anterior view, showing a naevus unius lateris of the chest, axilla, arm, forearm and hand. *B*, posterolateral view.

extending vertically downward just to the right of the median line. Laterally this plaque split into two bands, the lower of which extended horizontally around the chest and at the posterior axillary line expanded to form a large, somewhat ovoid patch with irregular margins and terminated in the midclavicular line posteriorly. The upper band extended a short distance laterally and upward, joined a broad band which extended laterally just below the axilla and ended at the lower angle of the scapula. This in turn joined an irregular patch occupying the medial aspect of the upper third of the right arm. On the hypothenar eminence and the

medial aspect of the wrist was another irregular patch, and there was a streak of lesions on the dorsal aspect of the terminal two phalanges of the fifth finger.

Treatment of the nevus consisted of surgical excision in five stages. The first four operations were performed at the Paterson General Hospital (December 16; Jan. 27, 1934; March 17, and April 7). In this series of operations the portions of the nevus occupying the chest wall and the axilla were removed. In the first three operations primary wound closure was carried out, but after the fourth operation Reverdin skin grafting was performed.

Fig. 9 (case 2).—Photomicrograph of a naevus unius lateris removed from the arm on Aug. 23, 1934, showing hyperkeratosis and distortion of the epithelial layers and papillae.

On August 23, at the Memorial Hospital, the remaining nevus on the arm was excised (fig. 9) and covered with Thiersch grafts, all of which took satisfactorily. This completed the removal of the growth (fig. 10), and the patient was observed at both the Paterson General Hospital and the Memorial Hospital at frequent intervals. There was no recurrence of the nevus.

After August 26 he was not seen until Jan. 27, 1937, when he appeared at the Paterson General Hospital, complaining of vomiting after meals for one week.

Fluoroscopic study after administration of barium sulfate revealed an obstructive lesion in the lower terminal portion of the esophagus. Removal of a biopsy specimen through an esophagoscope showed epidermoid carcinoma. Gastrostomy and a blood transfusion were done on February 1, and a series of roentgen treatments to the esophagus was instituted. However, on February 20 thrombosis of the right iliac artery occurred. The patient became rapidly weaker and died the following day, February 21.

A restricted postmortem examination showed the carcinoma also to involve the cardia and the greater curvature of the stomach, and there were metastases to the lymph nodes in the gastrohepatic ligament and to those about the pancreas.

CASE 3.—G. P. M., a 36 year old American-born white married man, was admitted to the Memorial Hospital on Nov. 6, 1932.

Fig. 10 (case 2).—Slight scarring after complete removal of the nevus in multiple stages (Sept. 26, 1934).

Since birth this patient had had a pigmented papillary nevus involving the right side of the trunk and the right upper extremity. The nevus caused no symptoms apart from bleeding on slight trauma, and there was no change in its appearance or extent until the spring of 1932, when several small areas on the shoulder and arm seemed to grow larger. On September 15 the patient noticed a small lump in the right axilla. Ten days later he began to suffer severe pain in this region. He also had sharp pain in the right side of the chest on coughing or sneezing. There was no hemoptysis, but he became dyspneic.

On October 26, in Pittsburgh, lymph nodes were removed from the right axilla. Dr. Ewing examined the specimen microscopically and made a diagnosis of metastatic epidermoid carcinoma.

Physical examination on admission to the Memorial Hospital on November 6 showed the right side of the shoulder girdle to be noticeably smaller than the left, and the right nipple was atrophied and retracted upward and outward. In the right

axilla was a recently healed surgical incision. Beneath this scar there was marked induration of the subcutaneous tissues and several hard nodes could be palpated. There was considerable telangiectasia of the skin of the right axilla from previous irradiation.

Limited for the most part to the right side of the body was a dark brown pigmented, papillary nevus. It was distributed on the trunk and upper extremity (fig. 11). From the sternal notch to the level of the nipple a vertical band extended down the median line, which sharply limited its left border. From the sternal notch the area spread laterally over the right clavicular region onto the anterior and superior aspects of the shoulder, which it covered in a capelike fashion. This area extended down anteriorly into the axilla and just above the nipple gave

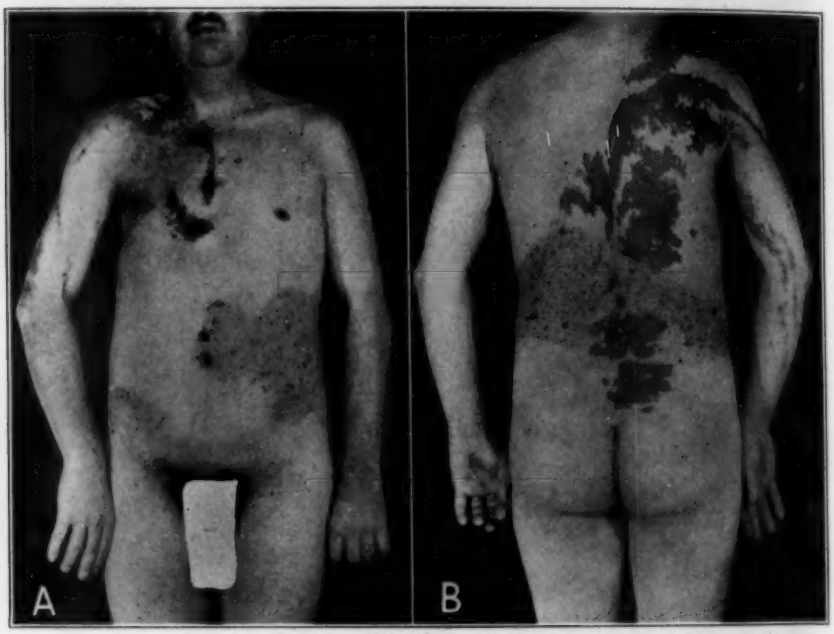

Fig. 11 (case 3).—Photographs taken Nov. 6, 1933. *A*, anterior view, showing the distribution of the naevus unius lateris. Note the atrophy of the right side of the shoulder girdle. *B*, posterior view. The site of malignant degeneration of the nevus cannot be seen in either view.

off a broad band, which passed downward and medially to terminate just to the right of the xiphoid process.

On the posterior aspect of the trunk the lesions extended a short distance to the left of the midline in the lumbar and interscapular regions. Largely covering the thoracic region and on the posterior aspect of the shoulder were several irregular patches, the upper portion of which joined the previously described area on the superior aspect of the shoulder. Irregular, continuous and interrupted streaks extended down all surfaces of the arm to the elbow, and a few streaks extended down the medial surface to the midpoint of the forearm.

In the upper part of the lumbar region posteriorly there was a broad band of skin which showed slightly increased pigmentation and in which were small, sparsely scattered lesions. There were also smaller similar areas in both groins. On the posterior and medial aspects of the right arm and in the right supraclavicular region were four small growths, which were firmer, more granular and suspected of being neoplastic.

Fig. 12 (case 3).—Photomicrograph of a nodule of recent development in a naevus unius lateris. The lesion is a typical basal cell carcinoma. The malignant tumor derivative of the naevus unius lateris is usually either a basal cell or a squamous cell carcinoma, practically never a melanoma.

Roentgen examination of the chest on entry showed multiple spherical opacities in the lungs, interpreted as metastases.

Biopsy of the aforementioned nodules in the skin was done on November 7. At the same time the axilla was exposed. The entire axilla was so densely

fibrotic that further exploration was not done. Microscopic examination of each of the four cutaneous nodules excised revealed pigmented basal cell epithelioma with adenoid features (fig. 12).

The patient was started on a course of low voltage roentgen therapy, but this had to be abandoned because of pain in the axilla and inability to lie on the table. He returned to his home on December 6 and died there on December 27. The location of the primary epidermoid carcinoma in the skin, which had metastasized to the axillary lymph nodes and to the lungs, was not found.

CASE 4.—H. C., a 24 year old American-born white man, came under observation at the Memorial Hospital on only one occasion, May 19, 1937, and never received treatment in any form.

Fig. 13 (case 4).—Photographs taken May 19, 1937. *A*, anterior view, showing the bilateral distribution of the nevus in the neck and the submental region. The tumor in the left temporal region can also be seen. *B*, posterior view.

Since birth there had been an extensive pigmented nevus on the left side of the body, which had never caused any symptoms and had not increased in area.

Physical examination showed a pigmented brown verrucous nevus sharply limited to the right side of the body except on the anterior aspect of the neck, where it was bilateral (fig. 13).

Beginning in the midsternal line was a vertical neval streak which extended downward in the median line, running an interrupted course and dwindling out midway between the xiphoid process and the umbilicus. Covering the umbilicus

was a rosette of papillary lesions, and from there a solid line of nevi extended down to the pubis.

Between the level of the left inguinal ligament and the left pectoral region was a series of four bands of lesions. Each band was composed of individual streaks and patches between which were areas of unaffected skin. These bands began at the midline and swept laterally and upward around the body to terminate posteriorly in irregular patches which came within 5 cm. of the median line. The lower band terminated at a level of the crest of the ilium. The middle bands, which began anteriorly at the umbilicus and xiphoid process respectively, fused posteriorly to form a single patch at the level of the costal margin. The highest band extended across the pectoral region and in the areola formed papillary growths.

Fig. 14 (case 5).—Lentiginous nevus. *A*, anterior view showing sharp limitation of the nevus at the median line. *B*, right posterolateral view. Note the involvement of the neck and upper part of the back.

It extended into the axilla and ended in the scapular region posteriorly. From this band isolated streaks extended onto the arm both anteriorly and posteriorly. On the posterior aspect of the shoulder were several scattered small groups, and near the median line of the back were several more isolated patches and lines, which extended down to the midlumbar region.

There was a transverse band of papillary lesions across the entire anterior aspect of the neck and the submental region. Posteriorly, however, the cervical lesions were confined to the left side, with one thick streak running down the median line to the level of the last cervical vertebra. In the left temporofrontal region was another scattered group of nevi.

OTHER NEVI OF UNILATERAL DISTRIBUTION

Two other conditions which are unilateral nevi but of the lentiginous type and therefore not considered suitable for this series are shown in figures 14 and 15. They had both been present since birth and had caused no symptoms. Biopsy of the nevus in another case (fig. 16) showed accumulations of pigment in the cells of the basal epithelial layer and some perivascular round cell infiltration of the corium.

Fig. 15 (case 6).—Lentiginous nevus, less pronounced than that in case 5 but also sharply demarcated at the median line.

ANALYSIS OF CHARACTERISTICS OF NAEVUS UNIS LATERIS

The cases of naevus unis lateris which have been reported in the literature, together with our own cases, have been reviewed with the purpose of determining the various characteristics of this unusual tumor. The criteria for determining the suitability of the cases have been: (1) verrucous or papillary nevi; (2) linear configuration of the lesions; (3) predominantly unilateral distribution, and (4) involvement of sufficient extent to make the peculiarity of essentially unilateral distribution self evident.

There were 156 cases in which the lesions fulfilled these criteria. These, with the addition of our own 4 cases, made a total of 160. In an analysis of the nevi the following factors have been taken into consideration: (1) race; (2) sex; (3) distribution or location of the nevus; (4) age incidence; (5) heredity; (6) pigmentation; (7) relation to nerve distribution; (8) histopathologic appearance; (9) symptoms; (10) treatment; (11) course of the disease, and (12) presence of other congenital abnormalities or other unusual features.

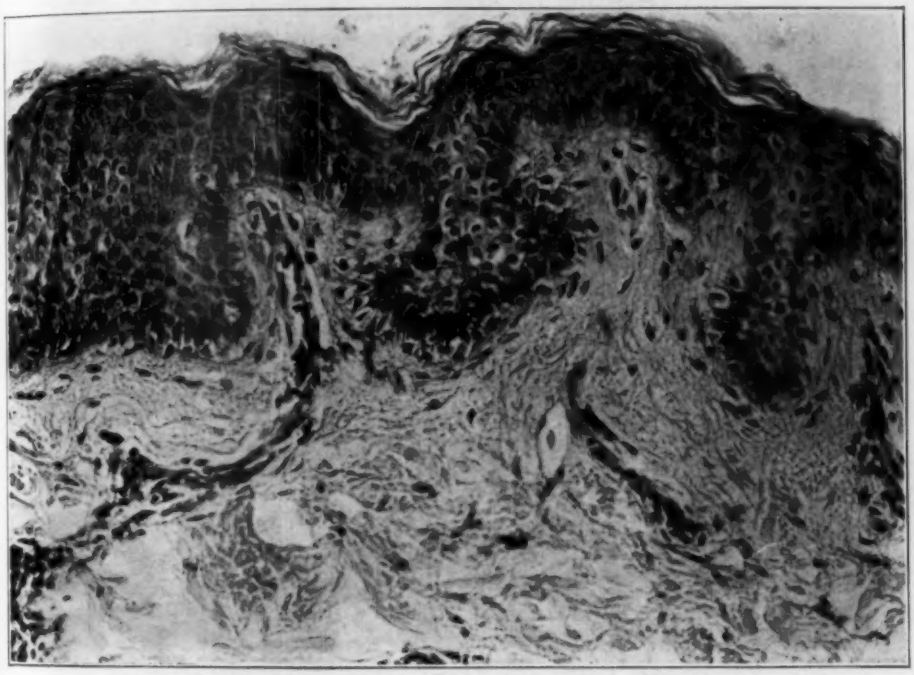

Fig. 16.—Photomicrograph of a section of nevus removed from the base of the neck. Increased pigment in the cells of the basal epithelial layer can be seen.

Race.—Hasselmann's patient [27] was a Filipino, and the author stated the belief that the nevus was the only one reported as occurring in a person of this race. It was an extensive pigmented nevus appearing at birth and involving the right side of the trunk, right thigh, leg and foot. The patient was a 13 year old boy. One Negro appeared in the series, his case being reported by Parounagian.[33] This patient had a verrucous lesion on the right side, involving the neck, axilla, shoulder, trunk, thigh, foot and leg. The age at which it appeared was not known. At the time

33. Parounagian: Initial Lesion of Lower Lip: Naevus Unius Lateris, J. Cutan. Dis. **29**:235, 1911.

of the report, the patient was 30 years old. Of the patients in the remaining cases, 1 was Cuban, 1 Spanish, 1 Hungarian, 1 German, 3 Italians and 4 Jews. In 93 of the other cases the patients were stated to be white. In the remainder they were presumably white and undoubtedly represented American, English, German, French and Russian nationality, as judged by the nationality of the authors.

Sex.—The sex of the patient was given in 156 cases, in which 78 patients were male and 78 female, an equal division.

Distribution or Location of the Nevus.—In 154 cases the side of involvement was stated. In 79 the nevus occurred on the left side of the body, and in 75, on the right side. In the male patients the left side was affected in 37 cases and the right side in 39 cases; in the female patients the left side was affected in 40 instances and the right side in 31. In short, in this series of cases there was equal involvement of the sexes; almost equal involvement of the two sides of the body in the group as a whole, and equal involvement of the two sides of the body in each sex. In 14 of the cases the nevus crossed the midline, but in no case was there sufficient crossing to mar the predominantly unilateral distribution.

For purposes of classifying the distribution of these nevi the body was arbitrarily divided into twelve portions: face and head, neck, axilla, shoulder, arm, forearm, hand, trunk, genitalia, thigh, leg and foot. The number of times each of these areas was involved in the 156 cases in this series is as follows: face and head, 40; neck, 55; axilla, 39; shoulder, 46; arm, 54; forearm, 37; hand, 26; trunk, 108; genitalia, 28; thigh, 59; leg, 42; and foot, 29. In 27 cases only one of these areas was involved: trunk, 11; face and head, 8; neck, 5, and thigh, shoulder and foot, 1 each. Two areas were involved in 33 cases. In 11 cases the lesions were limited to the face and neck; in 6 to the axilla and trunk; in 4 to the neck and trunk and to the trunk and thigh, respectively; and in 1 each to the axilla and shoulder, the arm and trunk, the genitalia and thigh, the neck and shoulder, the thigh and leg, the shoulder and trunk, the leg and foot and the face and trunk. In 34 cases three areas were involved, with no single outstanding group of areas. In 20 cases four areas were involved; in 14 cases, five areas; in 14 cases, six areas; in 5 cases, seven areas, and in 7 cases, eight areas. Of the 2 cases in which nine areas were affected, the face, neck and shoulder were spared in 1 and the axilla, shoulder and forearm in the other. In 1 case all areas were included except the hand and foot; in another only the hand and leg were omitted, and in 2 the lesions covered all areas.

In summary, the nevi in 94 of the cases, or 60.2 per cent of the series, were limited to three areas or less. In 22 cases they were limited to the head and neck; in 7 cases, to the upper extremity; in 5 cases, to the

lower extremity; in 17 cases, to the trunk alone (including the axilla); in 15 cases, to the trunk and upper extremity, and in 21 cases, to the trunk and lower extremity. There was no single area or group of areas of distribution which was sufficiently outstanding to indicate a single pattern of pathogenesis. However, the lesions of the trunk were arranged generally in a curving transverse band, except near the midline anteriorly or, less often, posteriorly, where the typical arrangement was in a vertical band sharply limited by the median line. The lesions of the extremities were almost always arranged in longitudinal streaks, often running a slightly spiral course. Nevi affecting the genitalia were sharply limited at the median line.

In several cases there were peculiarities of distribution. In Sequeira's case,[34] that of a pigmented nevus appearing at birth, distributed on the left side of the face, head and neck of a girl, showed involvement of the mucosa of the lip, buccal mucosa, gums and soft palate. Evans [35] also presented a case in which the lips, tongue and tonsils were affected. The lesion was a more extensive nevus, occurring in a male, limited to the left side of the body and including the face, head, arm, forearm, hand and trunk. Tobias [36] presented a case of a pigmented nevus, also of the left side of the face, head and neck of a girl, and appearing at birth, which likewise involved the left side of the tongue and the buccal mucosa. The patient also had partial hemiatrophy of the left upper and lower extremities. Two other cases in which there was intraoral distribution are that of Simon,[37] in which the hard palate, left tonsil and pharyngeal wall were affected, and that of Waelsch,[38] in which there was extension to the mucous membrane of the lower jaw and left cheek. Simon's patient was a girl with a pigmented nevus on the left side, limited to the head; Waelsch's patient was a male who had a pigmented nevus of the left side of the head and neck, dating from birth.

It is a strange coincidence, perhaps, that in all 5 of these cases the nevus was on the left side and that in 4 of them it was limited to the face, head and neck.

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34. Sequeira, J. H.: Case of Naevus Unius Lateris of Skin and Mucous Membrane, Brit. J. Dermat. **24**:313, 1912; Proc. Roy. Soc. Med. (Sect. Dermat.) **5**:201, 1911-1912.

35. Evans, W.: Case of Extensive Naevus, Brit. J. Dermat. **14**:263, 1902.

36. Tobias, N.: Nevus Unius Lateris, with Unilateral Hemiatrophy of the Left Side of the Body, Arch. Dermat. & Syph. **15**:83 (Jan.) 1927; Congenital Hemiatrophy Associated with Linear Naevus: Case, Arch. Pediat. **45**:673, 1928; Extensive Linear Nevus with an Associated Hemiatrophy, Arch. Dermat. & Syph. **18**:451 (Sept.) 1928.

37. Simon, T.: Ueber Nerven-Naevi, Arch. f. Dermat. u. Syph. **4**:24, 1872.

38. Waelsch, P.: Systematisierter ichthyosiformer Naevus, Arch. f. Dermat. u. Syph. **114**:237, 1912.

Age Incidence.—In 74 of the cases (46.3 per cent) the nevus was present at birth or appeared shortly thereafter. In 9 it appeared during the first year, and in 9, between the age of 1 and 2 years. One nevus appeared at 2 years of age; 4 at 3 years; 3 at 5 years; 2 at 8 years; 2 at 9 years; 1 at 12 years; 3 at 14 years; 1 at 16 years, and 2 at 17 years. In 1 patient the nevus appeared at the age of 46; this was a patient of Balzer and LeCornu.[39] The patient was a 47 year old man at the time of presentation and exhibited a right unilateral nevus of light brown pigmentation which was present on the neck, trunk, thigh and leg and was accompanied with no subjective symptoms.

In 13 instances, the nevi appeared at some time during childhood. In the remaining 35 the age of incidence was not given, but the upper limit of the possible age incidence may be deduced from the age of the patient at the time of presentation. In 11 the patients were below the age of 20, in 11, below 30 and in 5, above 30. In 8 cases neither the age of incidence nor the age of presentation was given.

A review of the ages of the patients at the time of presentation showed marked preponderance of the younger groups. Six patients were below the age of 1 year; 31 patients were less than 10 years of age; 47 patients were between 10 and 20; 37 were between 20 and 30; 14 were between 30 and 40; 7 were more than 40, and in 14 instances the age at the time of presentation was not stated.

Of the 7 patients over 40 years of age, 1 has already been mentioned. Of the remainder, 1 was presented by Okamura [23]; he was a 45 year old white man who exhibited a nevus on the right side, confined to the trunk, which appeared in childhood. Lasser's patient [40] was a woman 52 years of age whose lesion had appeared at birth, was limited to the right side of the body, was lightly pigmented and involved the axilla, arm, forearm, trunk, thigh and leg. The patient of Grütz [41] showed a nevus affecting the leg and foot, present at birth in a man who was 60 years old at the time of the report. Gerhardt's patient[11] was a 61 year old man who had been affected from birth by a pigmented nevus involving almost the entire right side of the body. In many areas this nevus was not pigmented. Jadassohn's patient [22a] was a 66 year old man with a nevus limited to the right thigh and the right side of the trunk; Luneau's [42] patient was a 45 year old man with a pigmented nevus limited to the right side of the trunk.

39. Balzer, P., and LeCornu, P.: Contribution clinque à l'étude des dermatoses, Ann. de dermat. et syph. **2**:929, 1901.

40. Lasser: Zur Therapie des Naevus verrucosus, Arch. f. Dermat. u. Syph. **33**:202, 1895.

41. Grütz: Psoriasis disseminata et verrucosa et linearis. Naevus verrucosus, Zentralbl. f. Haut- u. Geschlechstkr. **56**:230, 1937.

42. Luneau, H. G.: Des naevi systématisés, Thesis, Paris, no. 56, 1919.

Three patients showed peculiarities of onset of the nevus. In Sibley's patient,[43] a nevus affecting the axilla, shoulder, arm and trunk of an 18 year old girl appeared at the age of 5 years, following scarlet fever. Little's patient,[44] a 6 year old girl, at the age of 3 years had a "fit" followed by paralysis of the right leg. Three weeks later a pigmented nevus appeared on the left arm, axilla and trunk and remained unchanged until the time of presentation. In Geber's patient [45] a pigmented nevus appeared on the trunk and axilla six months after the patient was kicked by a cow. The injury caused periostitis and necrosis of bone, necessitating the removal of several fragments of bone from the ribs. It is doubtful whether these occurrences had more than a coincidental relation.

Heredity.—In 123 cases occurrence of nevi in the family was not mentioned. In 33 cases it was stated that there was no such occurrence. In only 4 cases was there any evidence of a hereditary factor. In the case of Samuel [46] the patient was a 26 year old woman who at the age of 16 had first noticed flat, warty lesions appearing on the chest and axilla. At the age of 25 the nevus began to appear on the neck and forearm. Her daughter, aged 9, was beginning to show similar nevi in the same location. The patient of Lesné, Clément and Boquien [47] was a 7 year old boy with a pigmented nevus on the left side, involving the arm, forearm, hand, trunk, thigh and leg, whose mother had also had a *keratose*. However, nothing further was known about her, because she had died. Omens [48] presented a 6 year old Jewess who had a pigmented nevus on the left side, involving the arm, trunk and thigh. Her mother had a large pigmented nevus involving the extensor surface of the left arm. Winkler's patient [49] was a 13 year old girl with a pigmented nevus appearing at the age of 6 months on the left thigh, leg and trunk.

43. Sibley, W. K.: Presentation of a Case of Naevus Unius Lateris with Unusual Effects of Solid Carbon Dioxide (Dermatitis Repens), Brit. J. Dermat. **25**:234, 1913; Proc. Roy. Soc. Med. (Sect. Dermat.) **6**:159, 1912-1913.

44. Little, G.: Naevus Zosterformis, Brit. J. Dermat. **17**:181, 1905.

45. Geber, cited by Neumann, I.: Ueber Naevus papillaris (Thompson) neuroticus, unius lateris (v. Bärensprung), neuropathisches Hautpapillom (Gerhardt), Nervennaevus- (Th. Simon), Oesterr. Jahrb. f. Pädiat. **8**:165, 1877.

46. Samuel, H. C.: A Case of Linear Naevus in a Mother and Child, Proc. Roy. Soc. Med. (Sect. Dermat.) **8**:126, 1914-1915.

47. Lesné, E.; Clément, R., and Boquien, Y.: Naevus hyperkératosique verruqueux et pigmentaire à disposition zoniformé, Bull. Soc. de pédiat. de Paris **30**: 448, 1932.

48. Omens, D. V.: Nevus Unius Lateris, Arch. Dermat. & Syph. **37**:922 (May) 1938.

49. Winkler: Fall von systematisiertem Naevus, Schweiz. med. Wchnschr. **51**: 137, 1921.

One brother had a yellow nevus on the right cheek, and her grandmother had a benign nevus on the leg which became malignant and caused her death.

Leven [50] presented the case of a young man with an extensive bilateral pigmented linear nevus of the trunk. Because of its bilateral distribution the nevus is not included in this study, but it is interesting from the point of view of heredity. The same lesion with the same distribution was presented by 2 older sisters. The remaining 6 siblings were not affected. Another interesting example of familial incidence not included in the study was cited by Bardach.[51] Identical female twins each had systematized, pigmented, bilaterally distributed nevi of the face, thorax and lower extremities. The lesions appeared simultaneously in the twins twenty-two months after birth.

Pigmentation.—Of the 156 nevi, 112 exhibited some degree of gross pigmentation which varied in degree from light yellow to dark brown or black. This pigment is largely exogenous, i. e., dirt, which invariably and inevitably accumulates in the papillary clefts of the tumor. In those regions where the tumor is constantly moistened with sweat, such as the axillas, groins, palms and soles, it assumes a pinkish white complexion, utterly devoid of traces of pigmentation. Under the microscope there is no increased pigmentation of the basal epithelial layer. The number of melanoblasts is not noticeably greater than normal, and true neval cells are absent. These facts are in accordance with the observation that the malignant derivatives of naevus unius lateris are either basal cell or squamous cell epitheliomas and not melanoma as might be supposed.

Relation to Nerve Distribution.—In 53 of the collected cases the tumors were considered by the authors to exhibit a configuration corresponding to the distribution of nerves. Two of the tumors were thought to follow cranial nerves; 25 were said to bear a distinct relation to spinal segments, and 20 were described as occurring along the cutaneous connections of peripheral nerves. Six tumors were believed to follow the lines of Voigt. Two tumors were thought to be related to cutaneous faults and one to follow hair lines. To the remaining (87) tumors no pattern of configuration could be applied.

In our own 4 patients the only peculiarity of distribution was that the nevi were arranged in a segmental manner. At first glance this would seem to agree with spinal nerve distribution. However, on close comparison of the distribution of the nevi with the course of the central and peripheral nerves, no constant agreement could be found in any case.

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50. Leven: Naevus linearis atrophicus et depigmentosus, Arch. f. Dermat. u. Syph. **140**:403, 1922.

51. Bardach, M.: Systematisierte Naevusbildungen bei einem eineiigen Zwillingspaar: Ein Beitrag zur Naevusätiologie, Ztschr. f. Kinderh. **39**:542, 1925.

The nevus of patient 1 covered an area innervated by the eighth cervical nerve, the first, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh and twelfth thoracic nerves and the first, second, third and fourth lumbar nerves. However, none of the areas was concurrent with a single zone of innervation, and no margins of the nevus corresponded to the boundary of distribution of the spinal nerves. The nearest approximation occurred in the distribution of the lesions of the forearm and hand (fig. 1 *C*). Here the streak on the forearm closely followed the course of the medial antebrachial cutaneous nerve (eighth cervical, first thoracic). From the wrist and over the palm of the hand and the volar aspect of the fourth and fifth fingers the distribution closely approximated that of the sensory branches of the ulnar nerve (also eighth cervical and first thoracic). However, here the analogy stopped, because the nevus extended medially to involve the medial aspect of the fourth finger and the lateral aspect of the third, an area supplied by the median nerves (fifth, sixth, seventh and eighth cervical).

In case 2 the nevus covered an area innervated by the eighth cervical nerve and the first, second, third, fourth, fifth, sixth, seventh and eighth thoracic nerves. In case 3 the area of distribution of the second, third, fourth, fifth and eighth cervical nerves, the first to twelfth thoracic nerves, the first, second and third lumbar nerves and the first and second sacral nerves was involved. In neither of these cases was there correspondence between the course of the nerves and the distribution of the nevus.

The correlation of nerve and nevus distribution was most suggestive in case 4. Anteriorly, the superior margin of the lesions of the trunk and arm coincided with the upper boundary of cutaneous distribution of the second thoracic nerve and inferiorly with the lower margin of cutaneous distribution of the twelfth thoracic nerve. However, between these points, except for their direct extension, there was little correlation between the bands of nevi and the cutaneous nerve segments. Posteriorly even the upper and lower limits did not correspond. The inferior patch extended over the distribution of the first, second and third lumbar nerves, and the upper portion of the nevus was irregularly scattered over the area of the fourth, fifth and sixth cervical nerves. The patch on the anterior aspect of the neck was in the region of the second and third cervical nerves and that in the frontal region in the area innervated by the trigeminal nerve.

In summary, no satisfactory correlation between nerve distribution and nevus distribution could be demonstrated in our 4 patients. Neither was there any occurrence with Voigt's lines or with any other known line.

Histopathologic Appearance.—The microscopic picture is surprisingly uniform. The most typical changes are marked hyperkeratosis, paraker-

atosis and slight acanthosis of the epidermis, with or without edema of the epithelial layers; increased thickness of the stratum granulosum and stratum spinosum; irregular elongation of the papillae, and round cell infiltration of the papillary layer and the corium. Hassselmann [27] and Matras [52] noted dilatation of blood and lymph vessels, and Morrow [2] only dilatation of lymphatics. Okamura [23] found numerous melanoblasts in the papillary layer. Callomon [53] and Polland [54] saw proliferation of sebaceous glands. In only 2 cases were nests of so-called nevus cells described (Ehrmann [55] and Polland [56]). These occurred in the papillary layer and in the corium. One section was thought by Becker and Obermayer [57] to resemble keratosis follicularis. Adamson [58] found a large vessel and nerve running in the subpapillary plexus, which he considered significant.

Microscopic sections of our tumors showed no marked variation from the pictures described by other authors. Papillary projection and convolution of the epidermis with distortion and elongation of the dermal papillae were striking and constant features. Hyperkeratosis was also marked. Edema of the epithelial layers was not pronounced, but there was marked variation in their thickness. In one or two sections rows or groups of cells extended from the basal epithelial layer into the corium and resembled nevus cells (fig. 3). The constant absence of groups of neval cells in these tumors is an important characteristic, distinguishing them from other true nevi. The tumor process therefore is essentially a congenital papillomatosis. Occasionally dense infiltrations of plasma cells and lymphocytes were seen in the corium. In none of the specimens was there increased pigmentation of the basal epithelial layer. The pigment of these lesions was apparently exogenous and could be seen in the overlying keratin. No changes were observed in the blood or lymph vessels.

Symptoms.—Only 14 patients in this collective review were reported to have any subjective symptoms. The most common complaint was

52. Matras: Naevus linearis unilateralis systematicus, Zentralbl. f. Haut- u. Geschlechtskr. **32**:181, 1930.

53. Callomon, F.: Systematisierter Naevus mit strichformigem Verlaufe in der Medianlinie, Arch. f. Dermat. u. Syph. **101**:221, 1910.

54. Polland, R.: Naevus linearis verrucosus, Dermat. Ztschr. **20**:499, 1913.

55. Ehrmann: Fall von systematisiertem Naevus, Arch. f. Dermat. u. Syph. **67**:282, 1903.

56. Polland, R.: Zur Lokalisation und Histologie der systematisierten Naevi, Arch. f. Dermat. u. Syph. **102**:101, 1910.

57. Becker, S. W., and Obermayer, M. E.: Nevus Unius Lateris, with a Microscopic Picture Resembling Keratosis Follicularis, Arch. Dermat. & Syph. **37**:102 (Jan.) 1938.

58. Adamson, H. G.: The Histology of a Case of Linear Naevus, Brit. J. Dermat. **18**:235, 1906.

itching, which occurred in 8 patients. In the patients of Hufschnitt [59] and Heidingsfeld [3] the itching was mild. In those of Fox,[60] Omens [48] and Lindenheim [28] the degree of discomfort was not noted. The remaining 3 patients suffered from severe itching. In Parkhurst's patient [61] the itching was constant, and secondary impetigo resulted from the scratching; Lane's [62] patient and Morrow's [2] patient suffered from severe itching, particularly after bathing. One boy, aged 5, presented by Wegge,[63] had "indefinitely described painful sensations." Barham's patient [64] complained of irritation of the face when shaving and irritation of the thigh and scrotum in hot weather. In the patient of Mackenzie [8] the lesions were irritable at night and caused marked scratching. The patient of Reckzeh,[65] a 12 year old boy with a nevus involving the axilla and trunk, suffered discomfort from the axillary portion being soft and moist. Another nevus of similar location (Frankovic [66]) caused a strong fetor. Finally, the patient of Ullmo,[67] a 20 year old woman with a pigmented nevus situated on the right side of the face, experienced a feeling of warmth on the affected side, although objectively there was no difference as compared with the left side. From this summary it seems evident that when symptoms occur at intervals in patients with these tumors, they are generally due to complications, such as infection, laceration and maceration by sweating.

Treatment.—The experience of any one physician, whether a dermatologist, a radiologist or a surgeon, has been so limited that no uniform or accepted plan of treatment has been devised. Thus, in reviewing this group of case reports, many bizarre forms of therapy have been employed without satisfactory results. For example, Sézary, Lefèvre and Rondinesco [68] gave eight autoinjections of blood, with supposed partial fading

59. Hufschnitt, G.: Vaste naevus de l'hémithorax et du bras gauche, Bull. Soc. franç. de dermat. et syph. **33**:305, 1926.

60. Fox, C.: Linear Naevus Papillaris, Brit. J. Dermat. **19**:258, 1907.

61. Parkhurst: Pruritic Nevus Unius Lateris, Arch. Dermat. & Syph. **14**: 625 (Nov.) 1926.

62. Lane: Nevus Unius Lateris, Arch. Dermat. & Syph. **18**:455 (Sept.) 1928.

63. Wegge, W. F.: A Case of Naevus Unius Lateris, Milwaukee M. J. **5**:191, 1897.

64. Barham, C. R.: Report of a Case of Naevus Unius Lateris, M. Rec. **43**: 200, 1893.

65. Reckzeh: Zwei Fälle von Naevus linearis unius lateris, Charité-Ann. **27**: 173, 1903.

66. Frankovic: Naevus pigmentosus papilliferus unilateralis systemisatus, Zentralbl. f. Haut- u. Geschlechtskr. **50**:354, 1935.

67. Ullmo, A.: Vaste naevus pigmentaire ardoisé de la moitié droite de la face, Bull. Soc. franç. de dermat. et syph. **40**:1516, 1933.

68. Sézary, A.; Lefèvre, P., and Rondinesco: Naevus pigmentaire linéaire, apparu à la puberté et évolutif: Action de l'autohémothérapie, Bull. Soc. franç. de dermat. et syph. **38**:651, 1931.

of a pigmented naevus unius lateris of the arm and forearm. Parenteral administration of arsenic has been resorted to empirically by Fordyce,[69] Lindenheim [28] and Plonski,[10] without lasting benefit. Strasser [70] used thyroid tablets, without improvement. It must be evident from the nature of the disease that medical measures which are accepted for the various keratoses and dermatoses will not be successful, as the lesion involves the entire thickness of the integument.

The aim of treatment is to remove the linear papillary nevus in its entirety and by so doing to overcome the cosmetic blemish it causes and to avoid the hazards of possible future malignant degeneration. In our opinion the only way to achieve this end result successfully is surgical excision and plastic repair either by undermining the skin sufficiently to effect primary wound closure by sliding flaps (case 2) or by skin grafting (case 3). This plan of treatment has been advocated by Alexander,[71] Calloman,[53] Galewsky and Schlossmann,[72] Gerhardt [11] and others. Earlier attempts at curettage were made, which removed the bulk of the tumor; recurrence inevitably followed because the basal layer of the skin persisted (Bleiman [73]; Ransom [74]). The application of solid carbon dioxide or cryotherapy has been suggested by numerous authors, among them Fordyce,[69] Gaskill,[75] Hufschnitt,[59] Little,[76] Roop [77] and Sibley.[42] Freezing causes the excessive papillomatous structure to slough off, leaving a cleaner base, but the improvement is only temporary.

Roentgen and radium therapy are never completely successful, although some improvement results with flattening of the nevus. Irradiation readily removes other varieties of hyperkeratosis and papillomatosis because of their superficial character; in the case of naevus unius lateris, however, the entire integument is involved. Radium or roentgen irradiation therefore can ameliorate but cannot cure this condition unless given to the degree of actual cauterization. The nevus involving the skin over the left breast of 1 of our patients (case 1) received roentgen

69. Fordyce: Naevus Verrucosus Linearis, J. Cutan. Dis. **37**:250, 1919.

70. Strasser, P.: Beitrag zur Kenntnis der systematisierten Naevi, Arch. f. Dermat. u. Syph. **66**:21, 1903.

71. Alexander, A.: Fall von Naevus linearis unius lateris, Dermat. Ztschr. **2**: 343, 1895.

72. Galewsky, E., and Schlossmann, A.: Ueber Naevus linearis, Deutsches Arch. f. klin. Med. **58**:85, 1896.

73. Bleiman, A.: Naevus linearis, J. Cutan. Dis. **26**:279, 1908.

74. Ransom, C. J.: Unusual Case of Naevus Unius Lateris, J. Cutan. & Genito-Urin. Dis. **14**:141, 1896; abstracted, Arch. f. Dermat. u. Syph. **45**:280, 1898.

75. Gaskill: Naevus Pigmentosus Unius Lateris, J. Cutan. Dis. **34**:232, 1916.

76. Little, G.: Two Cases of Naevus Unius Lateris, Brit. J. Dermat. **23**:83, 1911; Proc. Roy. Soc. Med. (Sect. Dermat.) **4**:64, 1910-1911.

77. Roop, W. O.: Naevus Verrucosus—Ichthyosis Hystrix, Arch. Dermat. & Syph. **37**:131 (Jan.) 1938.

therapy when she was 13 years of age; when she was 23 years old a true mammary carcinoma had developed in the same breast. This sequence of events may have been coincidental. The various authors who have used roentgen rays and radium are Fox,[78] Frankovic,[66] MacKee and Wise,[79] Sequeira,[54] and Tobias.[56]

Electrofulguration, electrodesiccation or surgical endothermy, with either the monopolar or bipolar coagulating or the cutting current, has had popular usage (Callomon [53]; Heidingsfeld [3]; Weissenbach, Lévy-Franckel and Carlu [80]). The method is inferior to sharp surgical excision unless the endotherm knife is used to remove the entire thickness of the tumor and the procedure is followed by surgical repair, i.e., suturing. Electrocoagulation, even when successful, is too frequently followed by excessive keloidal scarring.

Course of the Disease.—Unfortunately, the ultimate outcome in any case in this series was not given. The majority of the lesions remained stationary. Some tumors became more widespread after their initial appearance. The tumor in Frankovic's case,[66] which had been stationary since birth, began to show extension at the age of 22. A few tumors showed partial spontaneous regression, in 1 instance with subsequent recurrence (Heidingsfeld [3]). Only one of the nevi presented showed complete spontaneous disappearance without treatment. This patient, described by Bettmann,[81] was a normal boy, born at term. On the second day after birth he presented a systematized linear warty nevus involving the left side of the trunk (sharply demarcated at the median line) and the left arm and forearm. On the eighth day the horny character of the lesion was more pronounced; at reexamination, one month after birth, the lesion had spontaneously disappeared except for a short line on the forearm and an S-shaped line on the abdomen. Six months later every trace had disappeared. Koren's patient,[82] on whom the data were insufficient to justify inclusion in this series, showed spontaneous disappearance of the lesion. The patient was a boy 9 months old who at birth had a nevus involving the right forearm and hand. Grütz's patient [41] had a basal cell carcinoma in the region of the lesion on the thigh, which recurred after removal.

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78. Fox, H.: Presentation of a Case of Naevus Pigmentosus Unilateralis, Arch. Dermat. & Syph. **1**:467 (April) 1920.

79. MacKee and Wise: Naevus Verrucosus Linearis, J. Cutan. Dis. **34**:696, 1916.

80. Weissenbach, R. J.; Lévy-Franckel, and Carlu, L.: Naevus verruqueux géant de topographic dimidiée radiculaire: Electrocoagulation des placards cervicaux et des lésions de la face, Bull. Soc. franç. de dermat. et syph. **43**:406, 1936.

81. Bettmann: Spontane Rückbildung eines Naevus verrucosus unius lateris, Dermat. Ztschr. **20**:473, 1913.

82. Koren, cited by Galewsky and Schlossmann.[72]

Presence of Other Congenital Abnormalities or Unusual Features.—Gerhardt's patient [11] was epileptic. Hufschnitt's [59] patient lacked the lobe of an ear and had malformation of the teeth. The patient of Brocq and Rivet [83] evidenced more marked development of hair on the affected side of the body. Camptodactylia was present in the patient reported on by Sézary, Léfevre and Rondinesco.[68] Galloway [84] presented a patient with a nevus affecting the left side of the scalp and neck. There was imperfect formation of the outer canthus of the left eye, with incomplete separation of the cutaneous folds. The outer portions of both corneas were white. Meissner's patient [6] had poorer development of musculature and deficient hearing on the affected side. There was partial hemiatrophy of the upper and lower extremities on the affected side in the patient presented by Tobias,[36] and in Crocker's patient [85] there was associated pseudohypertrophic paralysis. Adamson's patient [86] had a supernumerary nipple. Reckzeh's patient [65] was feebleminded. The patient of Spiegelberg [87] showed association with hereditary syphilis. Strasser's patient [70] had a papilloma of the tongue. The nevus described by Spiethoff [88] occurred on the left side of the nose; the patient had a strabismus converging left and a congenital preputial midline defect. The father also had left strabismus. Müller's patient [14] exhibited a very extensive pigmented nevus covering most of the right side of the body. The right side of the scalp, even where not affected by the nevus, was covered by thin, long, blonde hair. The hair on the left side of the head was thick and black. Lewith's patient [89] had a tumor which involved the right side of the body. The right axilla perspired more than the left; the right half of the face was smaller; the right pupil was narrower; the nose pointed toward the right; the right breast was smaller, and the patient was left handed. The nevus in the case of Kudisch [9] was associated with total aplasia of the nuclei of both facial nerves.

Tobias presented a case [90] of nevus of the right thigh associated with lymphangioma of the vulva. He stated the belief that it was the only

83. Brocq, L., and Rivet, G.: Obstruction de naevus verrucosus unius lateris, Ann. de dermat. et syph. **4**:596, 1883.

84. Galloway: Naevus Unius Lateris, Brit. J. Dermat. **14**:57, 1902.

85. Crocker, H. R.: A Case of Papillary Growths in the Course of the Nerves, M. Times & Gaz. **1**:633, 1880.

86. Adamson, H. G.: A Case of Unilateral Pigmentary Naevus, Brit. J. Dermat. **23**:77, 1911.

87. Spiegelberg: Ueber einen Fall von angeborener papillomatöser sogenannter neuropathischen Wartzenbildung, München. med. Wchnschr. **43**:695, 1896.

88. Spiethoff: Strichformiger Naevus verrucosus, Zentralbl. f. Haut- u. Geschlechtskr. **18**:830, 1925-1926.

89. Lewith, R.: Ueber einen Fall von Naevus pigmentosus mit homolateralen nervösen Störungen, Arch. f. Dermat. u. Syph. **154**:69, 1927.

90. Tobias, N.: Lymphangiectatic Hypertrophy of the Vulva Occurring in a Nevus Unius Lateris, Arch. Dermat. & Syph. **8**:647 (Nov.) 1923.

case of association of these two conditions on record. The patient also showed smoothness of the right side of the tongue, which was thicker than the left, and a rough, scaly condition of the lips, sharply limited at the midline. The patient of Whitelocke and Rooth,[91] with a nevus affecting the left side of the trunk, the genitalia and thigh, presented in addition a fibroma of the left inguinal canal. The fibroma was removed.

Grütz's patient [41] apparently had psoriasis associated with the nevus, as did the patient of Philippson.[19] Adamson's patient [60] presented a pigmented papillary nevus of the left thigh and leg with a hemangioma in the same region. The hemangioma had been present at birth, but the nevus appeared later. Hallopeau and Weil [92] also presented a case of associated vascular and hyperkeratotic nevi, but the distribution was bilateral, and so it is not included in this series.

COMMENT

A survey of the literature makes it evident that the peculiarity of unilateral distribution is not limited to nevi of the verrucous or papillary type. As has been stated by many authors, a nevus may involve any of the components of the skin. Furthermore, papillary and verrucous nevi of systematic distribution may involve both sides of the body. These facts have led many authors to assume that all nevi of linear distribution should be classified as one group and that subdivisions according to distribution or according to the microscopic pathologic data are artificial and confusing. It is our opinion, however, that papillary or verrucous nevi of linear and unilateral distribution conforming to the criteria previously enumerated form a single clinical entity that is sufficiently characteristic to deserve individual classification to the exclusion of other forms.

Naevus unius lateris is manifested most commonly in the white race. There is equal involvement of the two sexes and of the two sides of the body in each sex. Nevi of limited distribution are more common than the more extensive type. There is no marked predilection for any single portion of the body. Lesions of the trunk are most frequently arranged in a transverse manner and those of the extremities in longitudinal or spiral streaks. However, there is no one characteristic pattern of distribution. (In this series only one third of the tumors showed any relation to nerve distribution.) In only rare instances is there any evidence of a hereditary factor. Almost half of the lesions appear at or shortly after

91. Whitelocke, A., and Rooth, J.: Case of Naevus Pigmentosus and Verrucosus, Brit. M. J. **1**:1027, 1902.

92. Hallopeau, H., and Weil, E.: Naevi systématisés métamériques, Bull. Soc. franç. de dermat. et syph. **8**:171, 1897; Ann. de dermat. et syph. **8**:483, 1897.

birth, and of the remainder the majority appear in early life. Over two thirds of the nevi show some degree of pigmentation. In some cases this is apparently due to increased pigmentation of the basal epithelial layer. In our own patients the pigment was exogenous. The microscopic picture of this type of nevus is fairly characteristic and consists chiefly of hyperkeratosis, distortion of the epidermis and elongation of the papillae. Nests of the so-called nevus cells are seldom, if ever, seen. Subjective symptoms are for the most part absent, and when they do occur they generally take the form of itching or irritation. Many forms of treatment have been employed, with varying degrees of success. We believe surgical excision of the entire thickness of the involved epidermis to be the method of choice. For extensive nevi this is necessarily done in multiple stages. Skin grafting may or may not be required, depending on the size of the area of skin removed.

The cause of the condition remains a vexing problem. The distribution of the majority of nevi shows no precise correspondence to that of central or peripheral nerves or to any of the various lines which have been described. On this basis alone, therefore, a case for causal relation to the nervous system cannot be made. In many patients, as in our own, there is segmental distribution which at first glance seems to coincide with nerve distribution; but on close analysis the relation does not hold. However, it must be remembered that there is often considerable overlapping of the peripheral terminations of separate cutaneous nerves and that segmental distribution is peculiar to the nervous (and skeletal) system in the adult human body. Furthermore, the trophic influence of nerves cannot be excluded as a factor in pathogenesis.

The pathologic process with this type of nevus appears to be located solely in the epidermis. It seems much more logical to assume that the distortion and elongation of the dermal papillae are secondary to the epithelial changes rather than their cause and therefore that the initial change occurs in the ectoderm rather than in the mesoderm.

The occurrence of skeletal malformations and epilepsy with naevus unius lateris has been interpreted by some authors as showing the relation of nevi to the central nervous system. The various coincidental malformations of the body collected from the literature and cited for the most part involved the nervous system and gave strength to this view. However, other systems besides the nervous system are involved, and, although various congenital abnormalities seem to appear more frequently in persons having nevi than in those unaffected, the possibility of mere coincidence cannot be completely discarded.

In summary, the cause and pathogenesis of naevus unius lateris are still unsatisfactorily explained. There is no universally apparent relation to the nervous system, but such a relation cannot be ruled out as the

prime etiologic factor. The microscopic and clinical pictures indicate primary involvement of the epidermis rather than the dermis.

It is generally known and has been stated many times that nevi may become malignant and that the form of malignancy which verrucous and papillary nevi take is not that of melanoma, but of epidermoid carcinoma. Tôyama and Kojima [93] reported a case of generalized verrucous nevi in which several basal cell epithelioma and one squamous cell carcinoma developed. By far the majority of the patients reported on are in the younger age group. It is unfortunate that the subsequent course of these patients is not reported so that the possible relation of the lesion to carcinoma may be determined.

In our own series of 4 cases, 3 of the patients died of cancer. In 1 of them (case 3) multiple basal cell carcinomas developed in the nevus. The axillary nodes were involved by epidermoid carcinoma, presumably metastatic from some undetected primary epidermoid cancer in the papillary nevus. The patient died of pulmonary metastases.

Another patient (case 1) died at the age of 23 from pulmonary metastases of carcinoma of the breast. The breast had always been smaller than its mate, had been covered with nevi and had received heavy irradiation. When the lesion was first noted it was believed to be a cutaneous cancer and to be due possibly to the irradiation. However, the microscopic picture of mammary adenocarcinoma precluded that possibility, as far as is known at present. The comparative youth of the patient, the presence of the nevus on the breast and the small size of the breast, all unusual circumstances, arouse speculation as to a possible causal connection between the nevus and the malignant tumor.

The third patient (case 2) died of carcinoma of the esophagus and stomach at the age of 43. Although in this patient the tumor developed at a younger age than the average, there is little basis on which to assume more than coincidental occurrence of the nevus and the carcinoma.

In conclusion, it should be emphasized that the relation of naevus unius lateris to carcinoma should be more thoroughly investigated and the patients followed over a period of years to determine malignant potentiality.

Additional references will appear in the reprints of the article.

93. Tôyama, I., and Kojima, R.: A Case of Verrucous Nevi Associated with Basal Cell Epitheliomas, Bowen's Disease, and Squamous Cell Epithelioma, Jap. J. Dermat. & Urol. **40**:116, 1936; abstracted, Arch. Dermat. & Syph. **36**:626 (Sept.) 1937.

HISTOLOGIC DISTRIBUTION OF VITAMIN A IN BIOPSY SPECIMENS OF THE LIVER

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The use of the fluorescence microscope permits the histologic visualization of vitamin A in tissues.[1] The results of recent investigations on the histologic distribution of vitamin A in the livers of human beings and of animals under normal and under pathologic conditions have been reported.[2] In these studies the human tissues examined were obtained at autopsy. Two objections may be raised against the results: 1. Postmortem changes may influence the picture, although no evidence of changes occurring in the first twelve hours after death was obtained in animal experiments. 2. The antemortem conditions and the irregular intake of food prior to death may influence the amount and the distribution of vitamin A. The purpose of this paper is to report on a study of the vitamin A fluorescence in specimens of human livers obtained at operation in order (1) to investigate the significance of the foregoing objections, (2) to examine the influence of the known preoperative nutritional state on the vitamin A content of the liver and (3) to evaluate the influence of hepatic function on the distribution of vitamin A when the factor of alteration of function prior to death was absent.

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1. von Querner, F.: Der mikroscopische Nachweis von Vitamin A in animalen Gewebe. Zur Kenntnis der paraplasmatischen Leberzelleinschlüsse, Klin. Wchnschr. **14**:1213, 1935. Popper, H.: Histological Demonstration of Vitamin A in Rats by Means of Fluorescence Microscopy, Proc. Soc. Exper. Biol. & Med. **43**: 133-136, 1940; Vitamin A: The Distribution of Vitamin A in the Body, J. Mt. Sinai Hosp. **7**:119-132, 1940.

2. (*a*) Popper, H., and Greenberg, R.: Visualization of Vitamin A in Rat Organs by Fluorescence Microscopy, Arch. Path. **33**:11-33 (July) 1941. (*b*) Popper, H.: The Histologic Distribution of Vitamin A in Human Organs Under Normal and Under Pathologic Conditions, Arch. Path. **32**:766-803 (June) 1941.

Vitamin A imparts a striking green fluorescence to the lipoids which carry it, the degree of fluorescence depending on the amount of the vitamin present. The fluorescence fades within a minute, because of the destruction of vitamin A by the ultraviolet rays used in fluorescence microscopy. The substance visualized by the characteristic fluorescence is not vitamin A itself but the fats made fluorescent by vitamin A. The specificity for vitamin A of this fluorescence in sections of fixed tissues has been demonstrated by various animal experiments.[2a]

MATERIAL AND METHODS

The patients selected for study received different types of diets. All of them consumed a known diet for at least eight days; no evidence existed for a reduced intake of vitamin A prior to this time. Two patients received 300,000 international units of vitamin A [3] twenty-four hours before operation. Patients with pathologic conditions of the liver were included; hence the distribution of vitamin A in our material cannot be used to judge the amounts of vitamin A in the livers of normal persons.

Specimens of the liver were taken in 29 cases in which the organ was exposed at operation. Part of the material was fixed in solution of formaldehyde and frozen sections were cut within thirty minutes; the other portion was fixed in Carnoy's solution and embedded in paraffin for routine histologic examination. The frozen sections, unstained and stained with phosphin 3R and methylene blue, were studied under the fluorescence microscope. The former dye is a sensitive lipoid stain. Methylene blue does not interfere with vitamin A fluorescence. By changing the ultraviolet filter to a ground glass filter the exact site of the fluorescence in the section stained with methylene blue could be determined in visible light.

RESULTS

Eleven of the 29 livers appeared entirely normal on gross and on routine histologic examination. The distribution of vitamin A fluorescence agreed with that in the livers obtained at autopsy.[2b] The fluorescence was observed in the Kupffer and in the liver cells. In the latter it was seen either in fat droplets, which were demonstrable with sudan III, or in fine lipoid droplets, which were demonstrable with phosphin 3R but not with sudan III. It was further seen in lipofuscin or diffusely dissolved in the cytoplasm. The vitamin A content of the liver cells paralleled that of the adjacent Kupffer cells. The distribution varied markedly in details, even in apparently normal livers. In pathologic specimens distinct variations were observed (table).

Total Amount of Vitamin A Fluorescence.—In 2 cases the vitamin A fluorescence was so marked that it could be observed with the naked eye. In both cases a large dose of a concentrate of vitamin A was administered a day before operation. The fluorescence was evenly distributed between the liver and the Kupffer cells (fig. 1 *A*). In the

3. The concentrate of vitamin A used was supplied by the Abbott Laboratories.

Results of Fluorescence Microscopic Studies and Routine Histologic Studies on Biopsy Specimens of the Liver Correlated with the Clinical Diagnosis

Diagnosis	Jaundice	Nutritional State	Interval Between Last Intake of Food and Operation, Hours	Damage of Liver Parenchyma	Pathologic Condition of Periportal Fields	Toxic Edema	Total Vitamin A Fluorescence	Homogeneous Distribution of Vitamin A	More Vitamin A in Kupffer than in Liver Cells	More Vitamin A in Liver than in Kupffer Cells	Lipoids Free of Vitamin A
Chronic cholecystitis and cholelithiasis.....	—	Obese	12	—	—	—	+	—	—	—	—
Calcification of gallbladder.....	—	Good	12	—	—	—	++	+	—	—	—
Cholelithiasis	—	Good	24	—	—	—	+++	+	—	—	—
Chronic cholecystitis	—	Good	18	—	—	—	+	—	—	—	—
Metastasis of pancreatic carcinoma to liver	+++	Poor	20	+	+	—	+	—	+	—	—
Chronic cholecystitis; diabetes mellitus.....	—	Obese	36	±	±	—	+	—	+	—	+
Carcinoma of stomach.....	—	Poor	2 days	+	—	—	±	—	+	—	—
Chronic cholecystitis	—	Poor	4 days	—	++	—	++	+	—	+	—
Cholangitis	+	Fair	24	—	++	—	++	+	—	—	+
Carcinoma of stomach.....	—	Poor	10 days	—	+	—	++	—	—	—	—
Chronic cholecystitis	—	.....	..	—	±	+	++	—	+	+	—
Chronic cholecystitis; perilobular cirrhosis..	—	Good	24	±	+++	—	+	—	+	—	—
Cholecystitis and cholelithiasis.....	±	Good	24	—	±	—	+++	+	—	—	—
Cholecystitis and cholelithiasis.....	—	Obese	24	—	—	—	+++	+	—	+	—
Cholecystitis and cholelithiasis.....	—	Good	24 *	—	—	—	++++	+	—	—	—
Chronic cholecystitis	++	Fair	16	±	+	—	+	—	+	—	+
Fibrosis of gallbladder.....	—	Poor	24 *	—	±	—	++++	+	—	—	—
Chronic cholecystitis; diabetes mellitus.....	—	Good	24	—	—	—	++	+	+	—	+
Chronic cholecystitis and cholelithiasis; diabetes mellitus	—	Poor	36	—	—	—	++	+	+	—	+
Penetrating peptic ulcer.....	—	Poor	12	+	±	±	+	—	—	—	—
Cyst of liver.....	—	Good	10	—	—	—	++	—	—	—	+
Carcinoma of stomach.....	—	Poor	8 days	—	++	—	++	—	—	+	—
Cholelithiasis	±	Good	24	—	—	—	++	—	—	—	—
Chronic cholecystitis and cholelithiasis.....	—	Poor	20	—	—	—	++	+	—	—	—
Toxic hepatitis	+++	Fair	17	+	++	—	+	—	+	—	—
Carcinoma of ampulla of Vater.....	+++	Fair	12	+	+	—	+	—	+	—	—
Stone in common duct.....	+++	Good	24	+	+	+	+	±	+	—	—
Carcinoma of pancreas.....	+++	Good	24	+	+	±	+	+	+	—	+
Hydrops of gallbladder; parenchymatous hepatitis.....	—	Obese	24	++	±	+	+	—	+	—	++

* The patient received 300,000 international units of vitamin A twenty-four hours before operation.

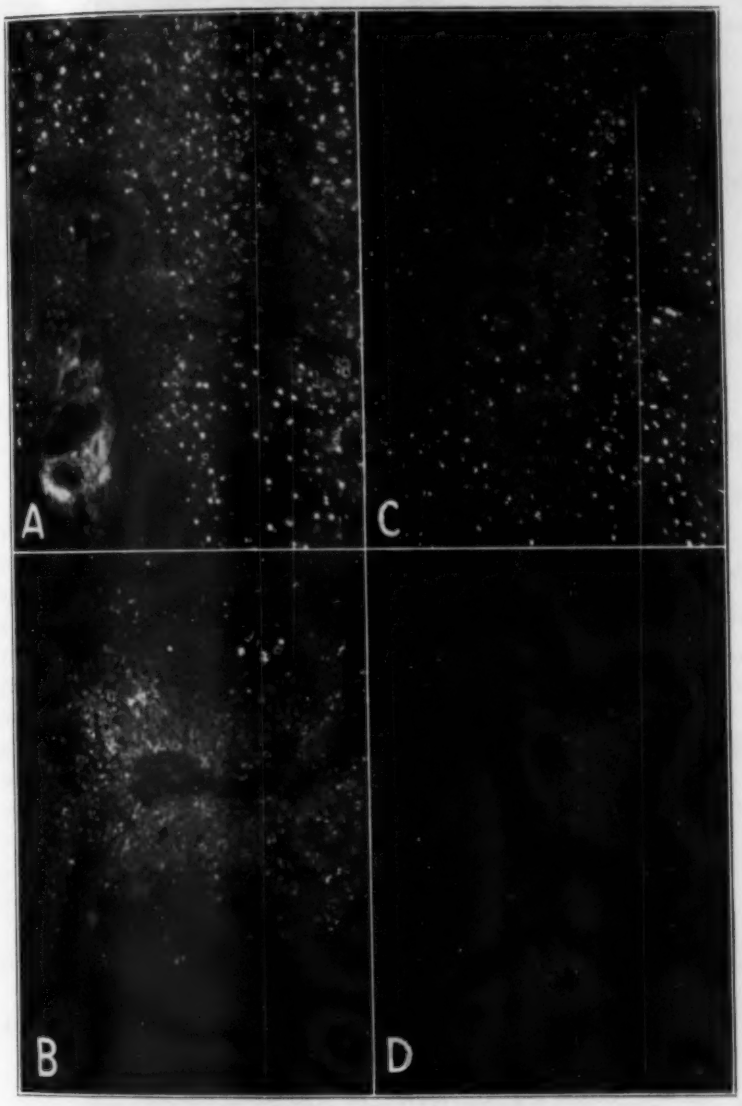

Fig. 1.—Fluorescence photomicrographs: *A*, liver with abundance of vitamin A fluorescence after oral intake of 300,000 international units of vitamin A twenty-four hours before operation. The Kupffer cells reveal high amounts of the fluorescence, and the liver cells contain many fine fluorescing droplets. *B*, liver showing strong vitamin A fluorescence imparted by the Kupffer and the liver cells, especially in the center of the liver lobule. *C*, liver showing average vitamin A fluorescence imparted by the Kupffer cells and by fine lipoid droplets and lipofuscin in the liver cells. *D*, traces of vitamin A fluorescence imparted chiefly by the Kupffer cells.

* The patient received 300,000 international units of vitamin A twenty-four hours before operation.

former it was imparted by fine lipoid droplets, which crowded the epithelial cells.

In 3 cases there were relatively large amounts of vitamin A fluorescence (fig. 1 *B*). The patients were in a good nutritional state. No damage to the parenchyma of the liver was apparent. In 1 case, in which there was subsiding jaundice, slight lymphocytic infiltration of the periportal fields was evident.

None of the 11 livers with average amounts of vitamin A fluorescence showed any pathologic change in the intralobular parenchyma (fig. 1 *C*). In 5, changes in the periportal fields, such as lymphocytic or leukocytic infiltrations, fibrosis or even moderate proliferation of the bile ducts, were observed. In 1 case there was slight jaundice. In most cases the liver cells were lined by fine lipoid droplets which imparted vitamin A fluorescence. The nutritional state of 5 patients was poor, as indicated by loss of weight and emaciation. Three had received no food containing vitamin A for four, eight and ten days, respectively, prior to operation, while they were fed intravenously.

Of 12 livers with small amounts of vitamin A fluoresence, 10 showed signs of damage to the parenchyma, such as central necrosis or necrobiosis, or necrosis of isolated liver cells. In 1 case there was perilobular cirrhosis with proliferation of the bile ducts and regeneration of the liver cells. Endothelial cells in the enlarged periportal fields imparted vitamin A fluorescence which is characteristic in cases of compensated cirrhosis [2b] (fig. 2 *A*). One liver showed definite parenchymatous hepatitis with fatty infiltration and dissociation of the liver cell cords. In 6 cases there was fully developed jaundice. In the area of hepatic damage the vitamin A fluorescence of the liver cells was completely absent, in contrast to its presence in the cells of the uninvolved parts of the liver lobule. The nutritional state of 2 of the 12 patients was poor. All 12 patients took food within thirty-six hours prior to operation.

Traces of vitamin A fluorescence were found in the liver of a patient who had carcinoma of the stomach with emaciation (fig. 1 *D*). Signs of hepatic damage were present.

No influence of age or of the type of anesthesia on the distribution of vitamin A was apparent.

Relation Between Fluorescence of Kupffer Cells and That of Liver Cells.—A characteristic picture of large amounts of vitamin A fluorescence in the Kupffer cells and reduction or absence of fluorescence of the liver cells may be seen either in the entire lobule or in part of it (fig. 2 *B*). Of the 13 cases in which it was encountered, the amount of fluorescence in general was not reduced in 3, in 2 of which diabetes mellitus was present and in 1 toxic edema. Among the other cases in which there was little vitamin A fluorescence were 6 in which there was

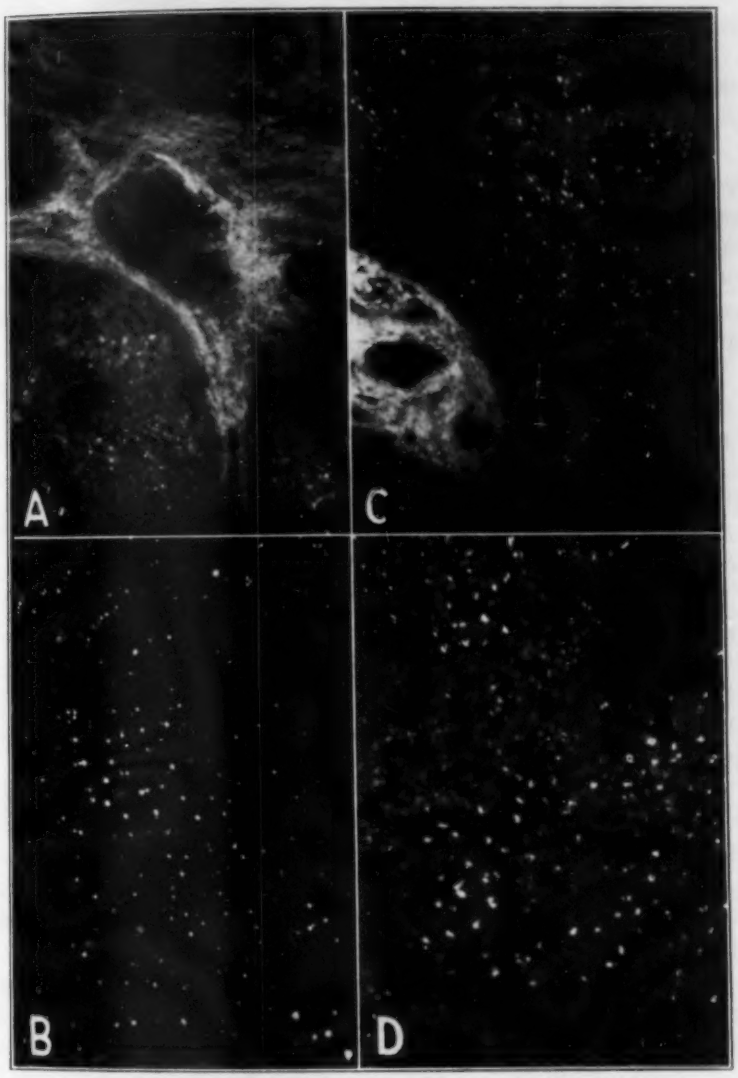

Fig. 2.—Fluorescence photomicrographs: *A*, perilobular cirrhosis. The little vitamin A fluorescence is imparted chiefly by the Kupffer cells. (The connective tissue of the proliferated periportal field gives a strong, nonfading blue fluorescence which appears white in the photomicrograph.) *B*, toxic edema of the liver. The Kupffer cells are rich in vitamin A fluorescence, while the liver cells are free of the vitamin A. *C*, jaundice. The area around the periportal field is free of vitamin A. In the intermediary zone the liver cells are free of vitamin A fluorescence, while the Kupffer cells contain a normal amount of vitamin A. *D*, diabetes mellitus. The Kupffer cells are rich in vitamin A fluorescence. The liver cells show small amounts, especially in lipofuscin.

fully developed jaundice. No influence of the nutritional state or of the interval since the last intake of food was apparent.

In 3 livers the Kupffer cells were poor in vitamin A fluorescence and there were normal amounts in the liver cells; in 2 of these the last food was taken four and eight days, respectively, before operation.

Distribution of Fat.—Usually, all lipoid droplets of the liver showed vitamin A fluorescence of varying degree. The amount of the fluorescence corresponded normally, therefore, with the amount of fluorescence produced by staining with phosphin 3R. Lipoids without vitamin A fluorescence were noted in 9 instances; they were especially evident in 1 case of parenchymatous hepatitis, in which there were large fat droplets with slight or no vitamin A fluorescence.

Lipofuscin.—Lipofuscin was represented by angular lumps of "wear and tear" pigment, located in the center of the cell; it imparted a red fluorescence which was visible after the fading of the vitamin A fluorescence. It was found, with and without vitamin A fluorescence, in various amounts in the liver cells and also in the Kupffer cells. No relation to pathologic change in the liver was noted. However, an increase in lipofuscin was apparent with increasing age.

Jaundice.—The increased bilirubin content was recognized by two phenomena: The cytoplasm of the liver cells imparted a dull green fluorescence, which was not altered by ultraviolet irradiation; and concentrated bile pigments, such as those in the bile casts or in the Kupffer cells in the center of the liver lobules, imparted no fluorescence and stood out as black spots. Such Kupffer cells were free of vitamin A.

In cases of fully developed jaundice the vitamin A fluorescence of the liver as a whole was reduced, the liver cells being poor and the Kupffer cells normal in fluorescence (fig. 2*C*). This picture was seen in 6 cases in which the icteric index was between 33 and 150 units. In the 3 cases of jaundice in which the icteric index was below 30 units, no reduction of vitamin A fluorescence was seen.

Toxic Edema.—In cases of toxic hepatic edema the interstitial spaces between the liver cell cords and the blood sinusoids are widened and filled with albuminous material. In 5 livers this picture was encountered, localized or evident throughout the lobule (fig. 2*B*). In the area of edema the liver cells lacked and the Kupffer cells were rich in fluorescence.

Diabetes Mellitus.—In 3 cases of diabetes mellitus a normal or reduced total amount of vitamin A fluorescence was observed. The vitamin A fluorescence of the liver cells was reduced, and that of the Kupffer cells was marked (fig. 2*D*). In the liver cells the vitamin A fluorescence was imparted by medium-sized fat droplets, which some-

times filled the entire cell. In 2 cases extensive glycogen degeneration of the nuclei [4] was seen. The cytoplasm in all 3 cases was rich in glycogen despite the extensive fatty infiltration. Apparently vitamin A fluorescence and glycogen may be seen in the same cell.

COMMENT

The study of the biopsy specimens of the liver offers additional evidence for the validity of the histologic demonstration of vitamin A. In animal experiments evidence was obtained for the specificity of the technic. The organs of vitamin A–deficient rats did not show the fluorescence. After the feeding of vitamin A or carotene the fluorescence reappeared in amounts which were in agreement with the doses fed and the chemical assay of the livers for vitamin A. The feeding of no other substance reproduced the fluorescence. This observation was extended to human organs by histochemical comparison of the fluorescence in human and in rat organs. The 2 cases of the present series in which extreme vitamin A fluorescence followed administration of a large dose of vitamin A concentrate offer similar evidence, although it is not as far reaching as that obtained in the animal experiments.

The histologic picture in the biopsy specimens agreed with that in the specimens of liver obtained at autopsy. The distribution of the fluorescence was the same. Some of the observations on the autopsy material [2b] were substantiated by those made on the biopsy specimens under better controlled conditions and without the complication of the agonal processes, namely, the reduced vitamin A fluorescence and the discrepancy between the amount of fluorescence in the Kupffer cells and that in the liver cells in cases of hepatic damage. This picture has been explained on the basis of inability of the epithelial cells either to hold vitamin A (with subsequent loss to the Kupffer cells) or to remove it from the Kupffer cells. Such a Kupffer cell-liver cell block was present in six cases of jaundice with hepatic damage, in 2 of uncomplicated toxic edema, in 1 of parenchymatous hepatitis, in 1 of cirrhosis and in 3 of diabetes mellitus. The block may be due to damage of liver cells; the presence of bilirubin may interfere with the storage of vitamin A; such interference is seen in the Kupffer cells which show an accumulation of bilirubin.

Clinical vitamin A deficiency in cases of diabetes mellitus has been reported [5] and explained on the basis of an inability of the liver to con-

4. Rosenberg, O.: Histologische Untersuchungen über das Leberglykogen, Beitr. z. path. Anat. u. z. allg. Path. **49**:284-312, 1911.

5. Brazer, J. G., and Curtis, A. C.: Vitamin A Deficiency in Diabetes Mellitus, Arch. Int. Med. **65**:90-105 (Jan.) 1940.

vert carotene to vitamin A.[6] The high glycogen content of the diabetic liver [7] cannot be responsible for this condition, since glycogen does not interfere with the storage of vitamin A in liver cells.

An absence of vitamin A fluorescence from the Kupffer cells can possibly be laid to a lack of food intake, since, according to the results of animal experiments, the Kupffer cells are the transfer station in vitamin A metabolism.

Our results suggest that the functional state of the liver cells determines the vitamin A content of the liver. In all cases in which pathologic change of the intralobular parenchyma of the liver was present, the vitamin A fluorescence of the liver cells was markedly reduced; and in nearly all cases in which the amount of vitamin A fluorescence was small, damage of liver cells was present. Pathologic changes in the periportal fields did not exert a decisive influence on the distribution of vitamin A. The low vitamin A content of the body in cases of hepatic disease was shown by chemical assay of the liver,[8] by the low level of vitamin A in the blood [9] and by ophthalmologic examination.[10] It was assumed that various causes [2b] were responsible for the reduced vitamin A content of the liver in cases of hepatic damage. In cases of localized hepatic damage the liver cells failed to show vitamin A fluorescence, in contrast to its presence in the intact areas. This indicated that not only impaired absorption of vitamin A from the intestinal tract, such as was shown by Breese and McCoord,[11] but the hepatic damage as such is responsible for the low vitamin A content of the damaged liver.

No definite influence of the nutritional condition or of the preoperative intake of vitamin A with the food was apparent, except for such extreme conditions as prolonged starvation or large doses of vitamin A concentrate before operation. Moderate emaciation or lack

6. Ralli, E. P.; Pariente, A. C.; Brandaleone, H., and Davidson, S.: Effect of Carotene and Vitamin A on Patients with Diabetes Mellitus: The Effect of Daily Administration of Carotene on the Blood Carotene of Normal and Diabetic Individuals, J. A. M. A. **106**:1975-1978 (June 6) 1936.

7. Popper, H., and Wozasek, O.: Zur Kenntnis des Glykogengehaltes der Leichenleber, Virchows Arch. f. path. Anat. **279**:819-868, 1931.

8. Moore, T.: The Vitamin A Reserve of the Adult Human Being in Health and Disease, Biochem. J. **31**:155-164, 1937. Breusch, F., and Scalabrino, R.: Die quantitativen Verhältnisse der Leberlipoide, Ztschr. f. d. ges. exper. Med. **94**:569-578, 1934.

9. Lasch, F.: Ueber den Vitamin-A-Spiegel im Blute bei Leberkrankheiten, Klin. Wchnschr. **17**:1107-1108, 1938.

10. Rissel, E.: Ueber Vitamin-A-Bildung bei Leberkrankheiten, Wien. klin. Wchnschr. **52**:214-218, 1939. Patek, A. J., Jr., and Haig, C.: The Occurrence of Abnormal Dark Adaptation and Its Relation to Vitamin A Metabolism in Patients with Cirrhosis of the Liver, J. Clin. Investigation **18**:609-616, 1939.

11. Breese, B. B., Jr., and McCoord, A. B.: Vitamin A Absorption in Catarrhal Jaundice, J. Pediat. **16**:139-145, 1940.

of food shortly before operation had no influence. This demonstrates that, with the exception of extremes, the vitamin A content of the liver is more influenced by the functional state of the organ than by nutrition. This is explained by the high storage of vitamin A in normal adults in comparison with the requirements. Many months on a vitamin A-deficient diet are required to deplete adult animals of vitamin A, and the same holds for adult human beings, according to adaptometric studies.

Since the vitamin A fluorescence may be an indication of the functional state of the liver, the fluorescence microscopic examination may be of help in the morphologic analysis of the liver, and the results of such an examination may represent a more sensitive morphologic criterion for hepatic damage than those of the routine histologic examination.

The liver is the most important vitamin A depot of the body; it stores about 95 per cent of the total of vitamin A.[12] The vitamin A fluorescence of the liver may thus indicate the vitamin A requirements of the organism. Our results suggest the importance of administration of vitamin A in cases of hepatic damage.

We intend to continue these studies and to compare the vitamin A stores of the body as determined by the vitamin A content of the liver with that determined on the basis of the level of vitamin A in the blood and on the basis of adaptometric readings in order to evaluate the clinical methods.

SUMMARY

The distribution of vitamin A in specimens of the liver taken for biopsy has been studied by means of fluorescence microscopy. The results substantiated those obtained from study of autopsy material. After intake of a large dose of vitamin A concentrate the fluorescence was strikingly increased. Otherwise, except for prolonged starvation, no striking influence of the nutritional state or the immediate preoperative intake of vitamin A on the vitamin A fluorescence of the liver has been observed.

Damage of liver cells leads to a reduction of the fluorescence, thus demonstrating the prevalence of the functional over the nutritional factors. A block in the exchange of vitamin A between the Kupffer and the liver cells has been found in cases of liver cell damage, jaundice, toxic edema and diabetes mellitus.

The fluorescence microscopic examination of the liver for vitamin A may help in the morphologic demonstration of damage of liver cells.

12. Sherman, A. C., and Boynton, L. C.: Quantitative Experiments upon the Occurrence and Distribution of Vitamin A in the Body, and the Influence of the Food, J. Am. Chem. Soc. **47**:1646-1657, 1925. Moore, T.: Vitamin A and Carotene: The Distribution of Vitamin A and Carotene in the Body of the Rat, Biochem. J. **25**:275-286, 1931.

HYPERTHYROIDISM AND ADENOCARCINOMA OF THE THYROID GLAND

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The repercussions of malignant disease on the function of the organ involved are vaguely understood. The effects on organs which secrete hormones are varied, but it is not beyond reason to assume that a malignant lesion originating in an endocrine gland can possess some of the same secretory properties as the benign epithelial tissue from which it derives. The thyroid gland may be the site of such a lesion. It has long been established that the active tissue in the thyroid gland is the epithelium, and frequently evidences of hyperthyroidism are reflected by morphologic changes in the thyroid epithelial cell. It is conceivable that the activity of the thyroid may be altered by the development within the gland of a malignant epithelial tumor or an adenocarcinoma. Because an accurate laboratory test exists to measure the activity of the thyroid gland, it is an ideal organ with which to evaluate the alterations in function accompanying primary adenocarcinoma. The association of hyperthyroidism, or hyperactivity of the thyroid, with primary adenocarcinoma of the thyroid gland is the subject of this essay. As will be seen, the factors involved and influencing this association include not only clinical variations but the coincident presence of other benign pathologic changes in the thyroid gland.

Conflicting reports are available concerning the association of carcinoma of the thyroid gland with hyperthyroidism and with exophthalmic goiter. Joll [1] and Simpson [2] have reported cases of carcinoma of the thyroid gland associated with hyperthyroidism. Crile [3] and Means,[4] however, have stated that in their experience the two diseases

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Portion of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Surgery.

1. Joll, C. A.: Diseases of the Thyroid Gland with Special Reference to Thyrotoxicosis, St. Louis, C. V. Mosby Company, 1932.

2. Simpson, W. M.: A Clinical and Pathological Study of Fifty-Five Malignant Neoplasms of the Thyroid Gland, Ann. Clin. Med. **4**:643-667 (Feb.) 1926.

3. Crile, G., Jr.: Hyperthyroidism Associated with Malignant Tumors of the Thyroid Gland, Surg., Gynec. & Obst. **62**:995-999 (June) 1936.

4. Means, J. H.: The Thyroid and Its Diseases, Philadelphia, J. B. Lippincott Company, 1937.

do not occur together. In an extensive article published in 1902, Ehrhardt [5] reviewed the literature on malignant lesions of the thyroid gland. He collected 5 cases of exophthalmic goiter associated with carcinoma of the thyroid gland and added 1 of his own. With the advent of tests for basal metabolism the diagnosis of hyperthyroidism has undoubtedly become more accurate. Elevation of the basal metabolic rate occurs in the presence of adenomatous goiter with hyperthyroidism and of exophthalmic goiter. In both conditions the performance of the accurate laboratory test available for measuring this rate is of diagnostic importance. Thus the determination of the basal metabolic rate in association with careful evaluation of clinical manifestations is likely to lead to a correct diagnosis in the majority of cases. With these factors in mind, a clinical pathologic study was undertaken in an effort to determine the relation of adenocarcinoma of the thyroid gland to hyperthyroidism.

MATERIAL STUDIED

In the cases studied a diagnosis of hyperthyroidism or of exophthalmic goiter was regularly corroborated by determination of the basal metabolic rate, beginning in the year 1917. This does not mean that a determination of the basal metabolic rate was made in every case of carcinoma of the thyroid, for it was obviously unimportant in cases in which there were no clinical signs of thyroid metabolic disturbances. From 1917 through 1937 there were at the Mayo Clinic 412 histologically proved and graded (Broders' method) adenocarcinomas of the thyroid gland. Only primary malignant neoplasms of epithelial origin were considered in this study. Each of the tumors was considered an adenocarcinoma, despite morphologic variations, such as scirrhous, papillary or malignant adenoma. Squamous cell epithelioma, despite the possibility that it arose from thyroid epithelium, was not included, since it was regarded as a metaplastic tumor. No significant change in function was noted in association with squamous cell epithelioma. Proliferating adenoma was not regarded as a separate entity but was classified as adenocarcinoma in an adenoma.

HYPERTHYROIDISM

Incidence.—A clinical diagnosis of hyperthyroidism was made in 57, or 13.8 per cent, of the 412 cases in which adenocarcinoma of the thyroid gland was found. All of the patients underwent operation, and all histologic studies were made on specimens obtained at operation. The frequency of occurrence of various typical symptoms of hyperthyroidism in these 57 cases is listed in table 1. Fixation of the vocal cords is

5. Ehrhardt, O.: Zur Anatomie und Klinik der Struma maligna, Beitr. z. klin. Chir. **35**:343-464, 1902.

listed merely to demonstrate how infrequently it occurred in these cases. This relative absence of fixation of the vocal cords indicates that tracheal structures were not infiltrated by the adenocarcinoma and that, as a result, the increased basal metabolic rate was due to metabolic increase in oxygen consumption rather than to mechanical obstruction as Branovacky-Pelech [6] suggested. Mechanical obstruction was not present in any case to cause dyspnea. In each of the 2 cases in which fixation of a vocal cord was found, only one cord was fixed, and in both the patients presented ample clinical evidence of hyperthyroidism. Chart 1 is the distribution polygon of the basal metabolic rates in the 57 cases of adenocarcinoma of the thyroid gland associated with hyperthyroidism.

TABLE 1.—*Incidence of Clinical Phenomena of Hyperthyroidism in Association with Adenocarcinoma of the Thyroid*

Clinical Manifestation	Cases
Nervousness	57
Palpitation	54
Loss of strength	53
Dyspnea	51
Tachycardia	50
Loss of weight	49
Tremor of extremities	47
Weakness of quadriceps muscle	42
Excessive sweating	29
Insomnia	26
Cardiac enlargement	21
Thrill or bruit	16
Edema	14
Headaches	14
Prominent eyes	14
Eye signs	10
Cardiac irregularity	10
Exophthalmos	9
Ocular pain	8
Vomiting	8
Diarrhea	8
Fixation of vocal cord	2

The lowest rate in this series of cases was + 8 per cent, and the patient presented definite clinical evidence to warrant a diagnosis of adenomatous goiter with hyperthyroidism.

Age and Sex.—Division of the patients with adenocarcinoma and hyperthyroidism into age groups revealed the following facts: The greatest number of patients was in the fifth decade of life at the time of operation. The average age in the entire series of 412 cases was 46.4 years, and in the 57 cases of hyperthyroidism it was 49.4 years. This seeming discrepancy is readily explained by the absence in the first two decades of life of hyperthyroidism associated with adenocarcinoma of the thyroid gland. When the figures are corrected for this factor the average age is about the same. The percentage of each age group in

6. Branovacky-Pelech: Ueber den funktionellen Wert der Langhansschen wuchernden Struma, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **39**:609-625, 1926.

which hyperthyroidism was associated with adenocarcinoma began at about 10 per cent in the third decade and rose to about 20 per cent in the seventh decade (table 2).

The evidence of hyperthyroidism was twice as great among women as among men.

Grade of Adenocarcinoma.—The greatest single key factor in the correlation of the pathologic characteristics of the lesion with the clinical symptoms seemed to be the grade of malignancy of the adenocarcinoma. A definite distribution by grade of malignancy was noted in the 57

TABLE 2.—*Age Distribution in Four Hundred and Twelve Cases of Adenocarcinoma of the Thyroid*

Age, Years	Total Patients	Without Hyperthyroidism		With Hyperthyroidism	
		Patients	Per Cent	Patients	Per Cent
0- 9	6	6	100.0	0	0.0
10-19	10	10	100.0	0	0.0
20-29	36	32	88.9	4	11.1
30-39	85	76	89.4	9	10.6
40-49	97	83	85.6	14	14.4
50-59	88	74	84.1	14	15.9
60-69	73	59	80.8	14	19.2
70-79	17	15	88.2	2	11.8
Average age	46.4	45.9		49.4	

TABLE 3.—*Distribution of Adenocarcinomas of the Thyroid by Grade of Malignancy*

Grade	Cases	Associated Hyperthyroidism	
		Cases	Per Cent
1	125	22	17.6
2	156	24	15.4
3	60	7	11.7
4	71	4	5.6

cases of adenocarcinoma of the thyroid associated with hyperthyroidism. According to Broders' method of grading, the adenocarcinomas, regardless of their morphologic structure, were divided into four grades. Grade 1 represents the least malignant group and grade 4 the most malignant group. The distribution of the 412 adenocarcinomas of the thyroid according to grade of malignancy and the percentage of adenocarcinomas of each grade associated with definite clinical hyperthyroidism are given in table 3.

Represented graphically (chart 2), the relation of the grade of the adenocarcinoma to the frequency of the hyperthyroidism is striking. Hyperthyroidism is much more frequently associated with the lower than with the higher grades of malignancy. Because the grade of the adenocarcinoma is a measure of its anaplasia, or of its degree of

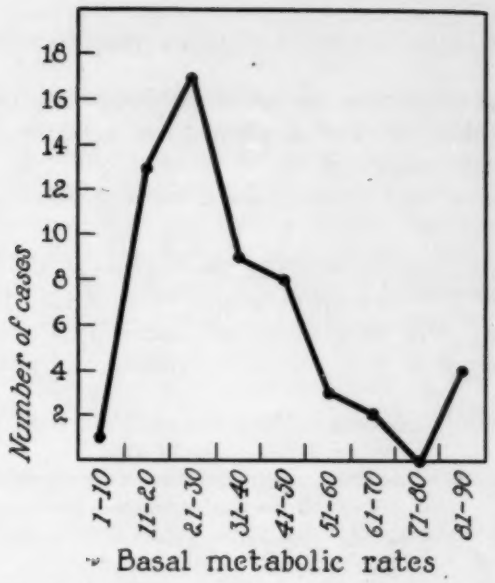

Chart 1.—Distribution of polygon of basal metabolic rates (plus per cent) in 57 cases of adenocarcinoma of the thyroid associated with hyperthyroidism.

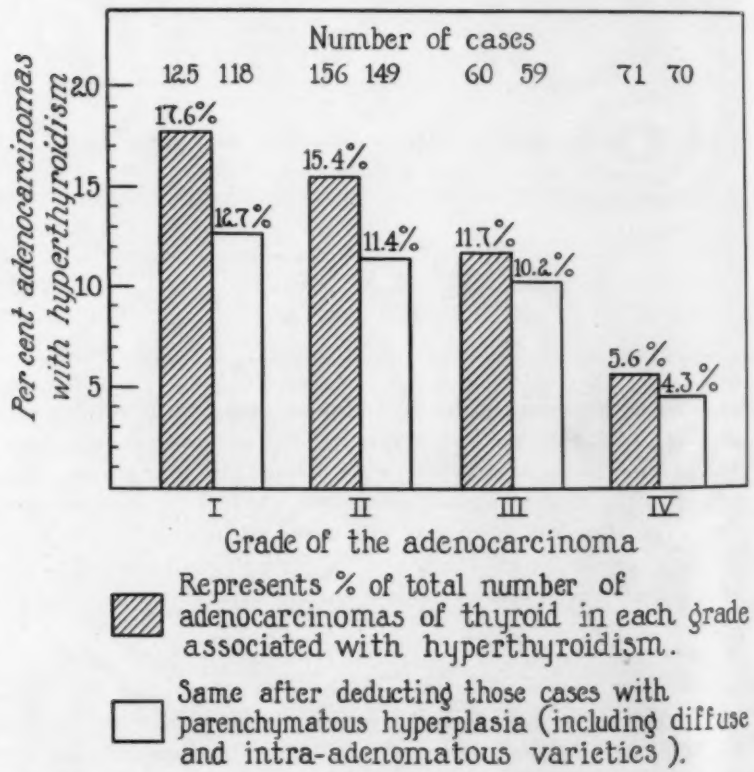

Chart 2.—Relation of adenocarcinoma of the thyroid to hyperthyroidism according to grade of malignancy.

malignancy, the inference may be drawn that for some reason the more malignant the tumor the less likely is it to be associated with any excess functional activity of the thyroid. The less malignant the tumor the more likely is hyperthyroidism to be associated with it; it cannot be said, however, that the more malignant the tumor the more likely is there to be a decrease in function of the thyroid. Myxedema in association with carcinoma of the thyroid gland, at least in cases in which treatment has not been given, is rare. There have been only 2 such cases at the clinic, and in both of these evidence of cretinism seemed to be present.

A morphologic distinction can be made for the papillary type of adenocarcinoma. The papillary adenocarcinomas in the series were of grades 1 and 2 except for 1 of the mixed type, which was graded 3. If the lower grades of adenocarcinoma are divided into a papillary and a nonpapillary type, a similar relation exists between the grade of malignancy and the frequency of associated hyperthyroidism (table 4).

TABLE 4.—*Distribution of Papillary and Nonpapillary Adenocarcinomas and of All Types of Adenocarcinoma of the Thyroid by Grade of Malignancy*

Type of Adenocarcinoma	Grade	Cases	Associated Hyperthyroidism	
			Cases	Per Cent
Papillary	1	83	11	13.3
	2	44	1	2.3
Nonpapillary	1	42	11	26.2
	2	112	23	20.5
All types	1–2	281	46	16.3
	3–4	131	11	8.4

With either type the increase in malignancy is associated with a decrease in the frequency of associated hyperthyroidism. The papillary type, although predominant in the lower grade, is not as frequently associated with hyperthyroidism as is the nonpapillary type.

If grade 1 is combined with grade 2 and grade 3 with grade 4, hyperthyroidism is found to be associated about twice as frequently with the lower grades of adenocarcinoma of the thyroid as it is with the higher (table 4).

Influence of Other Pathologic Features.—Other pathologic features in the thyroid gland must be considered as strongly modifying any hasty opinion which seems to derive inevitably from the foregoing implied relation between adenocarcinoma of the thyroid and hyperthyroidism. The benign gross and microscopic pathologic changes are significantly involved with functional variations of the thyroid gland. The presence of multiple adenomas in the thyroid gland frequently is associated with hyperthyroidism and gives rise to the well established syndrome of adenomatous goiter with hyperthyroidism. For this reason

it was deemed necessary to correlate with the grade of malignancy and hyperthyroidism the gross pathologic changes in the thyroid gland. The 412 cases of adenocarcinoma of the thyroid were divided into four groups according to pathologic changes found, as follows: those in which single nodules or adenomas were present; those in which multiple adenomas were present; those in which the carcinoma was so diffuse as to render the gland a homogeneous mass, and those in which no determination was possible because no operation other than removal of a biopsy specimen was performed. These groups were further subdivided according to grade of malignancy and according to whether clinical hyperthyroidism was present. The results of this reclassification are summarized in table 5.

TABLE 5.—*Frequency of Various Gross Pathologic Changes, Grade of Malignancy and Hyperthyroidism in Cases of Adenocarcinoma of the Thyroid Gland*

Grade	Hyperthyroidism	Single Adenoma	Multiple Adenoma	No Adenoma (Diffuse Adenocarcinoma)	Biopsy (No Determination Possible)	Total Cases
1	Absent	25	31	31	16	
	Present	5	14	2	1	
	Total	30	45	33	17	125
2	Absent	31	29	41	31	
	Present	4	14	6	0	
	Total	35	43	47	31	156
3	Absent	13	9	13	18	
	Present	1	3	3	0	
	Total	14	12	16	18	60
4	Absent	4	7	18	38	
	Present	0	2	1	1	
	Total	4	9	19	39	71
Grand total.....		83	109	115	105	412

When the relation of the gross changes was correlated with the absence or presence of hyperthyroidism, certain factors at once became evident. Hyperthyroidism was rarely associated with those adenocarcinomas for which only removal of a biopsy specimen was done. This may be due in part to the fact that less resection was attempted because of the absence of toxic symptoms. In most instances, however, a biopsy specimen was taken because the lesion could not be excised. Biopsy specimens were taken of only 13.6 per cent of the lesions of grade 1, but they were taken of 30 per cent of tumors of grade 3 and of 54.9 per cent of tumors of grade 4. In the 57 cases of hyperthyroidism biopsy specimens were taken in only 2, resection being carried out in all the others. Diffuse adenocarcinoma was present in 12 of these 57 cases (21.1 per cent), and it was impossible to note any adenomas in the glands.

Hyperthyroidism was present in 33 cases in which the thyroid gland contained multiple adenomas in addition to the adenocarcinoma. This is 57.9 per cent of all cases of adenocarcinoma of the thyroid gland associated with hyperthyroidism. The frequency of this occurrence indicates that some relation exists between hyperthyroidism and the presence of multiple adenomas. This observation is not surprising, since adenomatous goiter associated with hyperthyroidism is well established as a clinical and pathologic entity. The exact source of the hyperthyroidism in these cases has not been determined.

The significance of the presence of multiple adenomas in relation to adenocarcinoma of the thyroid associated with hyperthyroidism is at once realized from table 6. Two features may be noted in this table. The first is that the percentage of multiple adenomas associated with adenocarcinoma of the thyroid gland fell markedly with each grade as the grade of malignancy increased. The second is that in about half

TABLE 6.—*Adenocarcinoma of the Thyroid: Percentage of Cases of Multiple Adenomas in Total Group and in Cases of Hyperthyroidism*

Grade	Total Cases	Multiple Adenomas		Hyperthyroidism		
					Associated Multiple Adenomas	
		Cases	Per Cent	Cases	Cases	Per Cent
1	125	45	36.0	22	14	63.6
2	156	43	27.6	24	14	58.3
3	60	12	20.0	7	3	42.9
4	71	9	12.7	4	2	50.0

of the cases in which adenocarcinoma of any grade was associated with hyperthyroidism multiple adenomas were present in the thyroid gland. This does not mean that half the carcinomatous glands which contained multiple adenomas were also associated with hyperthyroidism.

In 24 cases multiple adenomas were not found and hyperthyroidism was present. The explanation of the source of hyperthyroidism in this group is most difficult to find, because the absence of multiple adenomas removes from the field of speculation the most obvious source.

In 83 (20.1 per cent) of the 412 cases studied the thyroid gland contained only a single nodule or adenoma. In 10 (17.5 per cent) of the 57 cases of hyperthyroidism a single adenoma was present in the thyroid gland. Apparently the presence of a single adenoma had no definite relation to the hyperthyroidism, since the percentage of cases of single adenoma associated with hyperthyroidism was slightly less than the percentage of cases of single adenoma in the 412 cases. The 10 glands in the aforementioned cases were studied in more detail in the hope that a clue to the relation to hyperthyroidism might be obtained.

The advantage with this group was that the rest of the gland could be considered as more or less eliminated from consideration of gross pathologic change. In 9 of the 10 glands the carcinoma was confined to the adenoma. In 1 other a diffuse papillary adenocarcinoma was found to be arising in or from a hypertrophic thyroid parenchyma.

In 8 of these 10 glands there was not visible any hypertrophy of the parenchyma to account for the symptoms of hyperthyroidism. The elimination of the factor of multiple adenomas in these glands in which adenocarcinomas were found and in which hyperthyroidism was an associated condition narrows the possible sources of hyperthyroidism to the malignant adenoma. The possibility that the adenocarcinomatous cells were in themselves the source of the hypersecretion and the hyperthyroidism is raised again.

TABLE 7.—*Type of Benign Parenchyma in Cases of Adenocarcinoma Associated with Hyperthyroidism*

	Cases
Multiple adenomas	33
Parenchymatous hypertrophy	11
Colloid parenchyma	22
Single adenomas	10
Parenchymatous hypertrophy	2
Colloid parenchyma	8
No adenomas and colloid goiter	5
No adenomas and parenchymatous hypertrophy	3
No evidence of any benign tissue	4
Biopsies	2
Total	57

Except in 2 cases in which operation was done only for removal of a biopsy specimen, the benign tissue of the 57 thyroid glands in which adenocarcinoma was associated with hyperthyroidism was studied histologically. In a few cases evidence of benign tissue could not be found despite the large quantities of tissue removed. As far as could be determined histologically, the parenchyma of the glands was apparently in a state of hyperactivity in 12 cases, and in 4 more cases intra-adenomatous hypertrophy was found. The type of benign parenchyma noted in the 57 cases of adenocarcinoma associated with hyperthyroidism is given in table 7. The apparent absence of any benign tissue in 4 of the 57 glands is an interesting point. Many years ago Carrell-Billard,[7] Ehrhardt and others noted that despite the absence of any microscopic evidence of benign tissue the function of the thyroid was maintained. Whether

7. Carrell-Billard, cited by Barthels, C.: Struma maligna, Ergebn. d. Chir. u. Orthop. **24**:162-325, 1931.

there is always a small portion of normal thyroid tissue remaining to maintain a normal supply of thyroxin cannot be determined.

The glands containing diffuse parenchymatous hypertrophy can be mentioned only briefly, but I should like to point out that in 7 of the 12 cases multiple adenomas were present.

COMMENT AND SUMMARY

The clinical variations in function known as hyperthyroidism are correlated with the presence of adenocarcinoma in the thyroid gland. The question of whether function and, therefore, hyperfunction can be attributed to adenocarcinoma of the thyroid gland is raised. By analogy, reports of hyperfunction associated with carcinomas of other endocrine organs, if applicable, would settle the question definitely in the affirmative. The infinitely varied and intricate pathologic changes occurring in the thyroid gland preclude such a clearcut conclusion.

TABLE 8.—*Distribution of Adenocarcinomas of the Thyroid by Grade of Malignancy: Cases of Parenchymatous Hyperplasia Omitted*

Grade	Number	Associated Hyperthyroidism	
		Cases	Per Cent
1	118	15	12.7
2	149	17	11.4
3	59	6	10.2
4	70	3	4.3

Although a definite conclusion that adenocarcinoma of the thyroid is the source of functional hyperactivity cannot be drawn from this clinical and pathologic study, the evidence points to the possibility that adenocarcinoma of the thyroid, like adenocarcinoma of other endocrine glands, at times and in part may perform the functional role of benign thyroid tissue. The inverse relation between the increase in malignancy and the decrease of frequency of hyperthyroidism seems especially significant. If a correction is made for cases of parenchymatous hypertrophy, because in these the source of the hyperthyroidism appears to be definitely located, then table 8 and chart 2 demonstrate that the fundamental relation between hyperthyroidism and the grade of malignancy still holds.

Only one other feature has been found to have a close connection with the relation of adenocarcinoma to hyperthyroidism, and that is the presence of multiple adenomas. As the grade of malignancy advances, the frequency of occurrence of multiple adenomas decreases, but about half the adenocarcinomas (of any grade) associated with hyperthyroidism occur in thyroid glands containing multiple adenomas. This is not

surprising, because the adenomatous goiter is likely to be associated with hyperthyroidism in a certain percentage of cases.

It is obvious, therefore, that in a majority of cases the benign gross and microscopic changes in the thyroid gland will eliminate quickly the adenocarcinoma as the only possible source of thyrotoxicosis. In some glands no such complicating factors are found. The hypothesis that an anaplastic tumor should retain less of the normal function of its constituent cells as the degree of anaplasia advances is an attractive one and has already been voiced by Ewing.[8] Some substantiation of this hypothesis may be inferred from this study of 412 histologically proved adenocarcinomas of the thyroid gland. The decrease in frequency of hyperthyroidism with the increasing degree of anaplasia seems to imply such a relation. Function, therefore, may be a property of adenocarcinoma of the thyroid gland and hyperthyroidism an adjunct thereof.

8. Ewing, J.: Neoplastic Diseases: A Treatise on Tumors, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

INGUINAL ECTOPIA OF THE OVARY AND FALLOPIAN TUBE

REVIEW OF THE LITERATURE AND REPORT OF THE CASE OF AN INFANT

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The occurrence in our service of a case of inguinal ectopia of the ovary and fallopian tube prompted us to make a survey of the literature. We have examined the reports to date to determine the incidence of this condition and the outstanding views as to its mechanism of development.

In our review of the literature we found several excellent summaries and compilations of cases. Among them, the reports of Andrews [1] in 1905 and 1906, those of Heineck [2] in 1912 and 1927 and that of Watson [3] in 1923 (revised in 1938) are excellent and complete analyses of reported cases. We decided to bring the compilation to the present, listing the aforementioned data as well as those reported since their publication. We have, however, attempted to restrict our list to cases of inguinal ectopia of the ovary and fallopian tube in an effort to distinguish the condition from simple ovarian and acquired tubo-ovarian hernia. This we found difficult because of the inadequate data given in some reports and the close similarity of these conditions.

We agree with Donald [4] that if the currently accepted embryologic mechanism is the correct one inguinal ectopia of the ovary, being congenital, is always accompanied with inguinal ectopia of the fallopian tube and is distinct from simple inguinal hernia of the ovary. It must be

From the Warren General Hospital.

1. Andrews, F. T.: Tr. Am. Gynec. Soc. **9**:407, 1906; Hernia of the Tube Without the Ovary, J. A. M. A. **45**:1625 (Nov. 25) 1905; Hernia of the Tube and Ovary, ibid. **47**:1707 (Nov. 24) 1906.

2. Heineck, A. P.: (*a*) Hernias of Ovary, of the Fallopian Tube, and of the Ovary and Fallopian Tube, Surg., Gynec. & Obst. **15**:63, 1912; (*b*) Hernies tubaires, ovariennes, et tubo-ovariennes inguinales et fémorales, Union méd. du Canada **56**:521 and 585, 1927.

3. Watson, L. F.: Hernia, ed. 2, St. Louis, C. V. Mosby Company, 1938.

4. Donald, D. C.: Ectopia and Inguinal Hernia of Ovary, Am. J. Surg. **47**:149, 1940.

admitted that some cases of tubo-ovarian hernia in our list were not instances of true ectopia of the ovary; but it is difficult to separate these in the literature.

ETIOLOGY

As has been pointed out by Donald [4] and Mauro,[5] there is a distinct difference between inguinal hernia of the ovary and inguinal ectopia of the ovary. With the former the ovary alone is found lying in the inguinal canal, while with the latter the ovary is accompanied with the fallopian tube. In both instances a persistence of the canal of Nuck and congenitally long ligaments of the ovary and tube play a role in the production of the abnormal position.

Up to this point congenital malformations predispose to both conditions. However, inguinal ovarian hernia is dependent on repeated increases in intra-abdominal pressure, e. g., pregnancies and possibly adhesions of the ovary to herniated mesentery or an intestinal loop (Mauro). This probably accounts for the occurrence of the condition in the older age groups. An associated anomaly of the internal genital organs may or may not be present.

The production of inguinal ectopia of the ovary is dependent on anomalous development of the genital tract. The presence of the ovary and the fallopian tube in the inguinal canal represents a full descent during fetal development and corresponds to descent of the testicle from an intra-abdominal to a scrotal position. Watson [3] stated that in his opinion there is not this similarity, "because testicle is retroperitoneal and ovary is intra-abdominal and has a free mesentery."

The mullerian duct and the mesonephric duct are intimately related in the first months of fetal life. Toward the third month the renal and the genital system are well separated and the ovary has reached the false pelvis. The ovary passes into the true pelvic cavity by actual and by relative descent, i. e., the relative differences in growth of the fetal body. Normally, the ovary stops in its descent because of the fixation of the gubernaculum of the ovary, the forerunner of the genito-ovarian (ovarian and round) ligament to the cornu of the uterus. The other end of the gubernaculum of the ovary reaches the base of the labium majus. The canal of Nuck, which extends into the labium majus at this point, usually becomes obliterated at the eighth month of fetal life. If, however, the canal of Nuck remains open, shortening of the distal end of the gubernaculum or the change in the relative growth of the parts, together with failure of attachment of the proximal end of the guber-

5. Mauro, M.: Contributo allo studio dell'ectopia e dell'ernia inguinale dell'ovaro, Arch. di ostet. e ginec. **41**:713, 1934; abstracted, Internat. Abstr. Surg. **60**:431, 1935; in Surg., Gynec. & Obst., May 1935.

naculum in time, causes the ovary to be pulled into the canal of Nuck lying within the open inguinal canal. The tube follows the ovary into the canal, since the proximal portion of the mullerian duct is closely associated with the ovary in its development. These features probably account for the evident frequency of inguinal ectopia of the ovary in the infant and for the frequent finding of a firmly adherent ovary and tube within the hernial sac. Of course, adhesions may be present, depending on the length of time the ovary and tube are allowed to remain in this position and subjected to trauma by trusses and pressure bandages. Heineck,[2b] in his second review of the literature, while distinguishing between acquired and congenital types of tubo-ovarian hernia, concluded that the tubo-ovarian hernia is the final state of tubal and ovarian hernia.

While the conclusions as to the causative factors are based on the known embryologic facts plus anomalies found at operation, additional, less definitely proved, factors undoubtedly play a role in their origin. As was suggested by Donald [4] and others, a hormonal imbalance occurring at a critical stage in the development of the generative organs may underlie the anomalous results.

It is interesting to note that maldevelopment of the internal genitalia is accompanied at times with anomalous changes in the renal system. Leisching [6] reported a case of strangulation of the left ovary, tube and broad ligament in the inguinal canal in which at operation the left kidney was found at the brim of the pelvis with its ureter 2½ inches (3.7 cm.) in length. Cullen [7] reported a case of bilateral inguinal hernia with a tube and an ovary in the right sac, an ovary in the left sac, absence of the left kidney and a right pelvic kidney.

Similarly, ectopia of the ovary is accompanied with additional maldevelopments of the genital tract. Montgomery [8] pointed out that the tube and ovary found in the sac of a congenital hernia are more common in the presence of a bifid uterus. Shackelford [9] reported a case of strangulation of the left ovary and tube in the inguinal canal in which there was a bicornuate uterus having a fully developed right cornu and an undeveloped left cornu. There were also two left kidneys, neither of

6. Leisching, A. C.: Strangulated Ovary in and Inguinal Hernia Associated with Congenital Abnormality of Kidney, Brit. M. J. **1**:993, 1929.

7. Cullen, T. S.: A Case of Right Pelvic Kidney with Absence of Left Kidney and Ureter, Both Ovaries in Inguinal Canals, Surg., Gynec. & Obst. **11**:73, 1910.

8. Montgomery, T. L.: Anomalies of Ovary, in Piersol, G. M.; Bortz, E. L., and others: Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, 1934, vol. 9, p. 424.

9. Shackelford, R. T.: Left Urogenital Maldevelopment, Am. J. Surg. **35**: 117, 1937.

which was in the renal fossa on that side. Rabinovitz [10] described a bilateral tubo-ovarian inguinal hernia with absence of the uterus and vagina. Shackelford [9] reported from the records of the Union Memorial Hospital and the Johns Hopkins Hospital 45 cases of incomplete development of the female generative organs. In this list there were 2 cases of left pelvic kidney and 1 case in which an ovary was present in a right inguinal hernia. Shackleford stated that in 8 of 140 cases of tubo-ovarian hernia there were deformities of the genital tract. He also cited Watson as having described 18 cases of bicornuate uterus in 56 cases in which the uterus was found in the sac of an inguinal hernia.

Morse, reviewing Mauro's paper,[5] stated that the diagnosis of inguinal ectopia should be considered when genital anomalies accompany the tubo-ovarian malposition. He stated that the most important criteria are the presence of a true sac containing the hernia, persistence of the canal of Nuck and genital defects of this canal. The most common are absence or underdevelopment of the uterus, unicornuate or bicornuate uterus and female hermaphroditism. Heineck [2b] also reported that it is not unusual to see malformations of the uterus, ovary and tube associated with this condition.

From an analysis of the literature it will be seen that further genital defects are not essential criteria for the diagnosis of inguinal ectopia of the ovary. In the great majority of the cases this condition is not associated with additional anomalies.

REPORT OF CASE

At the age of 4 months N. T., a well nourished girl, was treated for a swelling which appeared in the right inguinal region and extended into the labium majus. It was about 2 inches (5 cm.) in diameter, soft, slightly tender and readily reducible.

At the age of 8 months the patient was again seen, because of persistence of swelling in the same area. It had not become any larger, but there was an increase in the difficulty of reduction.

One month later the swelling recurred, becoming increasingly tender, and was associated with vomiting. Attempts to reduce the mass proved futile. Surgical intervention was then planned.

Surgical Procedure.—The patient was prepared for operation and was given a preliminary dose of 1/64 grain (1 mg.) of morphine sulfate with 1/300 grain (0.2 mg.) of atropine sulfate. She was then put under ether anesthesia. A Bassini type of incision was made, and the external oblique muscle was incised in the direction of its fibers; the internal oblique muscle was retracted medially, and the canal of Nuck was defined as patent, with a vaginal process of peritoneum extending completely through the canal of Nuck and adherent to the labium by many dense fibrous adhesions.

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10. Rabinovitz, M.: Double Ovarian Inguinal Hernia with Absence of Uterus and Vagina, M. Rec. **87**:586, 1915.

Dissection was difficult, because of the extremely fragile peritoneum. When it had been accomplished, the opened sac was found to contain the right ovary and fallopian tube. These structures were deeply cyanotic, moderately edematous and attached to the labium by a short gubernaculum of the ovary. When freed, it returned to the normal color promptly and was replaced in the abdominal cavity. The neck of the sac was approximately ¾ inch (1.9 cm.) in diameter and had probably contained omentum or a loop of bowel which had reduced itself spontaneously prior to the beginning of the operation. For this reason it was felt that the beginning strangulation of the tube and ovary was due to torsion and not to compression of structures at the neck of the sac. A high ligation of the sac was done with linen at the level of the deep epigastric vessels. The internal oblique muscle was sutured to the inguinal ligament over the canal with single interrupted no. 2 chromic catgut sutures. The remainder of the closure was done in the usual fashion.

Recovery was uneventful, and the patient was discharged in good condition on the eighth postoperative day.

FREQUENCY

In view of the recent distinction between simple inguinal ovarian hernia and inguinal ectopia of the ovary, analysis of past case records and compilations must necessarily lead to some inaccuracies when viewed in this light. While there is little difficulty in recognizing inguinal ectopia of the ovary when it occurs in an infant or a young child it is more difficult to diagnose when it occurs in an older person. When an older person presents a history of evident hernia since childhood, the hernia may be diagnosed as ectopia. So, too, when there is development of an inguinal mass after a strenuous effort or after childbirth without a preceding history of such a disturbance, the condition may be looked on as acquired even though it is evident that some congenital malformation is necessary to its production. Thus, in reanalyzing the literature and presenting the cases as we have done in the table, we have attempted to eliminate the really doubtful cases.

It is worthy of emphasis that the condition we are discussing is not as uncommon as it would seem. It is, we believe, reported infrequently. The diagnosis is not difficult in itself. It is necessary to keep it in mind as a possibility whenever an inguinal mass occurs in an infant girl.

In summing up the total number of cases to date in the world literature, we have examined previous summaries which did not distinguish between the forms of tubo-ovarian hernia which we have described. We have divided the total cases into those in which definite inguinal ectopia of the ovary appeared to be present and those in which there was a questionable element. We have been able to list 138 cases in the former and 57 cases in the latter group. This list includes practically all the cases reported since the latter part of the nineteenth century.

Analytic data on the age of the patient or the actual time when the condition was first noticed fall in line with the conclusion drawn by

Author	Age of Patient at Onset	Side Involved	Additional Data	Outcome
	Cases	Cases	Cases	Cases
1. Andrews [1] (82 cases up to 1906)	Under 1 year...31 1-2 years..... 3 2-5 years..... 6 5-10 years..... 4 10-20 years..... 3 20-40 years.....21 40 years..... 7 ?..... 7	Right..31 Left....41 Both... 5 ?..... 5	Strangulation or torsion..16 Other genital anomalies... 7 Cystic ovary..... 5 Ectopic pregnancy..... 4 Ovarian malignant growth 1 Intestine or omentum..... 6	Tube and ovary resected.51 Replaced.....20 ?..... 7 Autopsy..... 3 Death..... 7
2. Cullen [7]	8 years	Left	.....	Tube and ovary resected
	17 years (5 years previously on left, 3 years later on right)	Both	Left kidney and uterus absent; right pelvic kidney	Right ovary and left ovary and tube resected
	Cases	Cases	Cases	Cases
3. Heineck [3] (41 additional cases to 1912)	Under 1 year...12 1-2 years..... 6 2-5 years..... 2 5-10 years..... 3 10-20 years..... 5 20-40 years..... 8 40 years..... 2 ?..... 3	Right..14 Left....18 Both... 4 ?..... 5	Strangulation or torsion...6 Other general anomalies....6 Cystic ovary.....7 Intestine or omentum.....3 Uterus in sac.....6	Ovary and tube resected.30 Replaced..... 7 ?..... 4
4. Coley and Hoguet (1912), cited by Cohn: New Orleans M. & S. J. **80**: 723, 1928	9 cases	?	Found in 8,589 hernias of all types at Hospital for Ruptured and Crippled	?
5. Whitelock: Brit. J. Child. Dis. **10**: 353, 1913	Infant	Right	Intestine	Replaced
6. Eustace and McNealy: J. A. M. A. **62**: 772 (March 7) 1914	6 months (first noticed at birth)	Right	Torsion of ovary, tube and broad ligament with strangulation	Ovary and tube resected
7. Daniels: Beitr. z. Geburtsh. u. Gynäk. **18**: 312, 1913	31 years; present for 5 years	Right	None	Ovary and tube removed
8. Barr: J. A. M. A. **62**: 451 (Feb. 7) 1914	12 years; present for years	Right	None	Ovary and tube replaced
9. Rabinovitz [10]	35 years	Bilateral	Absence of uterus and vagina	?
10. Hodge: Ann. Surg. **44**: 958, 1906	2 months	Right	None	Ovary and tube removed
11. Cuff: Brit. M. J. **2**: 629, 1918	12 weeks; present since birth	Right	None	Ovary and tube replaced
12. Müller: Ann. Surg. **67**: 380, 1918	5 months	Left	None	Ovary and tube removed
	Same patient 5 weeks later	Right	.....	Ovary and tube replaced
13. Young: New Zealand M. J. **17**: 91, 1918	6 months	Right	Strangulation of tube, ovary and broad ligament	Resected
14. Ludington: New York M. J. **111**: 986, 1920	19 months; present since age of 1 month	Left	Uterus, both ovaries and tubes, broad ligament and knuckle of intestine	All organs replaced

11.	Cuff: Brit. M. J. **2**: 629, 1918	12 weeks; present since birth	Right	None	Ovary and tube replaced
12.	Müller: Ann. Surg. **67**: 380, 1918	5 months	Left	None	Ovary and tube removed
		Same patient 5 weeks later	Right	.....	Ovary and tube replaced
13.	Young: New Zealand M. J. **17**: 91, 1918	6 months	Right	Strangulation of tube, ovary and broad ligament	Resected
14.	Ludington: New York M. J. **111**: 986, 1920	19 months; present since age of 1 month	Left	Uterus, both ovaries and tubes, broad ligament and knuckle of intestine	All organs replaced
15.	Hollopeau and Colleville: Bull. Soc. anat. de Paris **17**: 336, 1920	2 months	Left	Torsion of pedicle of tube and ovary with strangulation	Ovary and part of tube removed
16.	McClanaghan: Tr. Am. Pediat. Soc. **33**: 362, 1921	2½ months; noticed bilaterally at 5 weeks	Both	Tube and overy on the left had some strangulation	Tube and ovary replaced on the left
17.	Abelio, in discussion on McClanaghan	3 months	?	Intestine also present	?
18.	Summers, in discussion on McClanaghan	2 infants	?	?	?
19.	Bertaux: Bull. Soc. anat. de Paris **20**: 764, 1923	7 months	Left	Strangulation of ovary and tube; operation under local anesthesia (procaine hydrochloride)	Ovary and tube removed
20.	Simmons, cited by Cohn: New Orleans M. & S. J. **80**: 723, 1928	3 years; 1 year duration	Right	None	Replaced
21.	Long, cited by Cohn: New Orleans M. & S. J. **80**: 723, 1928	3½ months	Left	Uterus also present	?
22.	Harper, cited by Cohn: New Orleans M. & S. J. **80**: 723, 1928	4 to 5 months	?	Strangulation of ovary	?
23.	Daggett: Brit. M. J. **2**: 346, 1925	7 weeks	Right	Strangulation of ovary; partial cleft palate	Reduced
24.	Dunet and Rousset: Presse méd. **33**: 106, 1925	3 months	Right	Quadruple torsion of pedicle of ovary and tube	Excision
25.	Buquet: Paris chir. **15**: 298, 1925	2 years	Left	Tube and ovary strangulated; inguinal hernia on other side	Resected
26.	Rowley: Am. J. Obst. & Gynec. **10**: 709, 1925	81 days; mass at birth	Right	Right and left ovary and tube in sac; ovaries cystic	Replaced
27.	Rochet and Peycelon: Lyon méd. **136**: 459, 1925	10 months; present at birth	Right	Volvulus of ovary and tube	Ovary and tube removed
28.	Touro Infirmary, cited by Cohn: New Orleans M. & S. J. **80**: 723, 1928	3½ years	?	?	?
		25 years	?	?	?
		34 years	?	?	?
29.	Bruner: Atlantic M. J. **30**: 280, 1927	6 months	Left	Ovary and tube twisted and gangrenous; cornu of uterus in ring	Ovary and tube removed
30.	Cohn: New Orleans M. & S. J. **80**: 723, 1928	6 months	Right	Pedicle twisted 5-6 times; round ligament short	Ovary and tube removed; round ligament had to be cut
31.	Graffagnino, in discussion on Cohn	5 years; present since birth	Left	None	Replaced
32.	Leisching: Brit. M. J. **1**: 993, 1929	5 years; present since birth; wore truss for 2 years	Left	Ovary, tube and broad ligament strangulated and gangrenous; left kidney at brim of pelvis; left ureter 2½ inches long; torsion present (tube and broad ligament)	Ovary and tube resected

Inguinal Ectopia of the Ovary and Fallopian Tube—Continued

Author		Age of Patient at Onset	Side Involved	Additional Data	Outcome
33. Wakeley: Surg., Gynec. & Obst. **51**: 256, 1930 (period 1916-1929)....	1.	1 year 2 months	Right	None	Reduced
	2.	4 years	Right	None	Reduced
	3.	4 years 9 months	Left	None	Reduced
	4.	1 year	Left	None	Reduced
	5.	2 months	Right	None	Replaced
	6.	1 year 4 months	Right	None	Replaced
	7.	6 months	Right	None	Replaced
	8.	2 years	Left	None	Replaced
	9.	2 years	Right	None	Replaced
	10.	4 years 4 months	Right	None	Replaced
	11.	9 months	Right	None	Replaced
	12.	3 years	Right	None	Replaced
	13.	47 years	Right	None	Replaced
	14.	7 months	Left	None	Replaced
	15.	8 years	Right	Acute torsion of ovary	Ovary removed
	16.	3 years 5 months	Left	None	Replaced
	17.	45 years	Right	None	Replaced
	18.	29 years	Left	3 months pregnant	Replaced
	19.	53 years	Right	Loop of intestine; acute torsion of ovary	Ovary removed
	20.	55 years	Right	Ovary twisted and adherent to sac wall	Ovary removed
	21.	1 year 3 months	Right	None	Replaced
	22.	1 year 1 month	Left	Uterus also present in sac	Ovary removed
34. Cepecchi [13]		6 months; present at 4 months of age	Left	None	Reduced
35. Mauro [5]	1.	42 years; duration 8 years	Left	Hydrocele and intestine present	?
	2.	42 years; present since childhood	?	Omentum present	?
36. Rush and Rush: Am. J. Surg. **29**: 140, 1935....		6 weeks	Left	Ovary and tube incarcerated	Reduced
37. Shackelford [9]		35 years; present for 12 years	Left	Ovary and tube strangulated; bicornuate uterus; left side undeveloped; atrophic ovary; two left kidneys	Left tube and ovary and uterine cornu excised
38. Vial and Bergeron: Rev. méd. de Nancy **67**: 116, 1939....		41 days	Left	Strangulation of tube and ovary	Tube and ovary removed
39. Donald [4]		26 years, since age of 7 years	Left	Strangulation of ovary, tube, mesovarium and round ligament	Tube, ovary and mesovarium removed
40. Mayer and Templeton....		8 months	Right	Strangulation of tube and ovary	Reduced

Heineck,[28] Watson [3] and Wakeley,[11] in that the majority, or 64 per cent, of the patients were under 2 years of age and 71 per cent were under 5 years of age. When all the cases were considered, the percentage became 46 per cent under 2, and 50 per cent under 5, years of age. This is not unlikely, in view of the congenital nature of this condition.

Interest in determining whether there is a tendency for this condition to be more prevalent on the left side was stimulated by the opinion held by Bland,[12] who stated that involvement of the left side is much more frequent in cases of inguinal hernia of the ovary. We were not able to conclude that this would hold true for inguinal ectopia of the ovary. We found that among 125 cases in which the pathologic process was taken to be inguinal ectopia and in which the side involved was listed, in 51 (41 per cent) it occurred on the right side; in 61 (49 per cent), on the left, and in 13 (10 per cent), on both. In 14 cases the side involved was not given. Of 57 unconfirmed cases in which the side involved was specified, in 53 per cent the condition occurred on the right and in 47 per cent on the left. In 14 unconfirmed cases the side involved was not stated. These figures lead us to the conclusion that there is no particular predilection for the left side.

In considering the problem of associated anomalies, it was found that of the total 195 patients listed, only 3 had maldevelopments of the renal system; 14 had abnormalities of the genital system, such as bicornuate uterus or absence of the uterus or vagina, and 2 had associated changes occurring in the two systems simultaneously. The cases listed are not likely to include all the possible cases, since in the vast majority exploration of the peritoneal cavity was not possible, the surgical procedure being restricted to the hernial sac and its contents.

From these data one cannot approve the contention of Montgomery [8] that the condition discussed "is more common in the presence of a bifid uterus."

The most common complication found was torsion or strangulation of the tube or the ovary or both. This occurred in 40 instances. A loop of intestine or omentum was present in the hernial sac in 15 cases. Changes in the ovary, such as cystic degeneration, were noted in 15 cases. Ectopic pregnancy in the ectopic tube occurred 5 times.

The percentage of cures, i. e., those resulting in the preservation of the tube, the ovary or both, is more favorable in the light of more recent reports. The totals taken to date show 56 cases in which the genital organs were saved and 102 instances in which a radical measure,

39. Donald[4]	36 years, since age of 7 years	Left	Strangulation of ovary, tube, mesovarium and round ligament	Tube, ovary and mesovarium removed	
40. Mayer and Templeton	8 months	Right	Strangulation of tube and ovary	Reduced	

11. Wakeley, C. P. G.: Hernia of Ovary and Fallopian Tube: A Record of Twenty-Five Cases, Surg., Gynec. & Obst. **51**:256, 1930.

12. Bland, P. B., and First, A.: Displacements of Ovaries, in Piersol, G. M.; Bortz, E. L., and others: Cyclopedia of Medicine, Philadelphia, F. A. Davis Company, 1934, vol. 9, p. 425.

i. e., removal of one or both structures, was required. In 5 cases the organs on one side were resected and those on the other side preserved.

There is no literature available at present to indicate whether the return of the partially damaged ovary and tube is an unwise procedure. The possibilities of cystic degeneration of the ovary and of ectopic (tubal) pregnancy in the damaged structures have been mentioned in support of the radical procedure.

The mortality rate in the reported cases has been very low. No deaths have been reported since the initial compilation of Andrews.[1]

DIAGNOSIS

Inguinal ectopia of the ovary is probably more common than the number of reported cases leads one to believe. Its diagnosis may be either simple or difficult, depending on the age of the patient and on the presence or absence of complications.

The diagnosis is made by palpating a firm mass, reducible or not, in the inguinal canal or in the labia. Auscultation reveals no peristaltic sounds. Rectal examination discloses a band (the fallopian tube) stretching from the inguinal ring of the inguinal canal to the cornu of the uterus. Vaginal examination shows displacement of the uterus toward the affected side. Manipulation of the uterus causes movement of the ovary in the canal.

In an infant the labial or inguinal swelling may be present without symptoms. The mass may be readily reducible and nontender, later becoming irreducible and tender. In the former state it must be distinguished from:

1. Inguinal hernia containing bowel or omentum. This is a swelling resonant to percussion and reduced with the characteristic gurgling sound. If it is omentum in the inguinal hernia, these characteristics are not present and the diagnosis is more difficult. There is more apt to be some gastrointestinal disturbance, e. g., constipation, nausea or vomiting.

2. Cyst of the labium majus. This is fixed and not reducible. The rectum and vagina are normal. The mass may be translucent.

3. Cyst of the canal of Nuck. This also is irreducible, translucent and fluctuant.

4. Dermoid cyst of the canal of Nuck. This is irreducible and firm. It may not transmit light.

5. Lipoma. Lipoma is firm, lobulated, asymptomatic, irreducible and opaque to light.

6. Lymphatic enlargement. This may be due to a systemic condition, e. g., lymphatic leukemia, or to a local condition, such as an infection.

In the adult the symptoms are more severe. The ovary in its abnormal position becomes very sensitive. This is accentuated during menstruation. Examinations will reveal a picture similar to that observed in the infant. However, the ovary is less likely to be reducible, because of adhesions to the hernial sac. Vaginal examination reveals a uterus displaced toward the same side as the hernia.

COMPLICATIONS

Like other structures at a foreign site, the ovary and tube are subject to complications. The most common are strangulation and torsion of the pedicle. In addition, there may be cystic degeneration, malignant change in the ovary, salpingitis or tubal ectopic pregnancy. Complicating the picture further, there may be involved with the tube and ovary some other organ, such as the bowel, the mesentery or the uterus.

In the acute phase the following conditions must be considered:

1. Abscess in the labia. This is difficult to distinguish from strangulation of the ovary and tube or torsion of its pedicle, because of marked tenderness and swelling of the adjacent tissues. Rectal and vaginal examination may be of help.

2. Strangulated hernia of the bowel. Watson stated that intestine is present in about 15 per cent of irreducible hernias of the ovary and tube.[12] When both are present the diagnosis is extremely difficult and is dependent on surgical exploration. However, in differentiating strangulated hernia of the bowel from strangulated hernia of the tube and ovary or from torsion of the ovary and tube in the presence of inguinal ectopia the following factors are important:

With the latter conditions (*a*) the general condition of the patient remains good; (*b*) there is no obstruction to the passage of gas; (*c*) on rectal examination the fallopian tube may be palpated passing to the internal inguinal ring, and (*d*) vomiting is reflex, does not have a gastrointestinal origin and subsides in a few days. It never becomes fecal.

3. Inguinal adenitis. The primary site of infection must be looked for. There is a febrile reaction.

TREATMENT

The treatment of inguinal ectopia of the ovary is surgical. It is impossible to determine the number of cases in which the ectopia has been reduced without surgical aid and the reduction permanently maintained. We have found no such cases reported in the literature.

As has been illustrated in several case reports, the hernia and its contents have been retained by means of trusses and pressure bandages for a short time, but these progressed to subsequent strangulation or torsion. Torsion a comparatively frequent complication, particularly in infants.

The surgical procedure is similar to that used for inguinal hernia. The sooner surgical intervention is undertaken, the better the prognosis. The general prognosis remains good at a late stage, even though the symptoms of torsion or strangulation may have persisted for eight to twelve days.[13]

The preservation of the ovary and tube is particularly important, since in the majority of cases the patients are under the age of 2 years. In the preservation of the tube, which may be somewhat damaged, there is the possibility that it may become the site of an ectopic pregnancy during the child-bearing period.

Whenever possible the tube and ovary are returned to the peritoneal cavity and the hernia closed in the usual manner. However, resection of the tube and ovary was found necessary in the majority of the cases reported in Heineck's [2a] compilation. Of 90 tubo-ovarian hernias, only 14 were reduced. Since that time, in 51 new cases, 31 have been successfully reduced.

The reasons given for resection of the ovary and tube were: (1) complete destruction of the tube and ovary due to torsion and strangulation; (2) malformation of the ovary and tube; (3) ovary and tube being irreducible because of their size; (4) presence of hydrosalpinx or pyosalpinx; (5) atrophic or cystic conditions of the ovary, and (6) neoplasm of the ovary.

For infants, general anesthesia has been found most satisfactory. For adults, spinal and general inhalation anesthetics have been used, depending on preference.

The prognosis is good, and in recent times the mortality has been negligible.

SUMMARY

1. Inguinal ectopia of the ovary is distinguished from inguinal tubo-ovarian hernia.

2. The etiology of this condition is reviewed.

3. A case of true ectopia of the ovary in an infant is presented.

4. A review of 195 cases is reported from the literature.

CONCLUSIONS

1. In the majority of cases inguinal ectopia of the ovary occurs in the first two years of life.

2. There is almost equal distribution as to the side involved.

3. Early surgical intervention with replacement of the organs is the best plan of treatment.

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13. Cepecchi, E.: Sullo strozzamento e sulla torsione del pedunculo nelle ernie tubo-ovariche congenite, Policlinico (sez. chir.) **37**:490, 1930; abstracted, Internat. Abstr. Surg. **52**:243, 1931; in Surg., Gynec. & Obst., March 1931.

GYNECOLOGIC MORTALITY

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This paper presents a review of the deaths in the gynecologic service from July 1, 1930 to July 1, 1940. A critical study was made of each surgical death in an effort to tabulate factors and faults in the preoperative preparation of the patient, in the operation and in the postoperative course that might have contributed to the fatal result, in order to avoid such mistakes in the future if possible.

Statistics on hysterectomies done in this service have for some years been carefully compiled and reported.[1] Table 1 is a composite table showing the incidence and death rate of this operation for approximately the same period covered by the mortality figures. Hysterectomy of one type or another was done on about 30 per cent of the patients operated on.

The organization of the gynecologic department for these ten years was simple from the surgical standpoint. The personnel of the private service consisted of twelve operators and a radiologist and was a constant group. That of the ward, or staff, service, being organized on the residency system with a senior supervisor, consisted of three operators per year, some of whom were changed at the end of each year. However, no house officer performed a major operation by himself until his fourth or fifth year of hospital training, and then he operated only after a period of supervision.

CLASSIFICATION OF DEATHS

From 1930 to 1940, 147 deaths occurred in the gynecologic service. The general plan of grouping fatalities followed by Marshall and Thompson[2] was used in this study except that all the records seemed to fall more readily into two main groups than into three. For simplicity it was decided to keep these two groups quite separate in the discussion, with a more detailed analysis of the second group (deaths following elective operations).

From the Department of Obstetrics and Gynecology, the Maternity Hospital, and the Western Reserve University.

1. Faulkner, R. L.: Hysterectomy: A Clinical and Statistical Study, Ohio State M. J. **32**:229 (March) 1936. Weir, W. C.: Statistical Report of 1,914 Cases of Hysterectomy, Am. J. Obst. & Gynec. **42**:285 (Aug.) 1941.

2. Marshall, H. K., and Thompson, R. H.: Mortality Lessons in a Series of 4,029 Gynecologic Operations, California & West. Med. **45**:263 (Sept.) 1936.

Group 1.—This group, of 84 cases, includes instances of death from malignant tumor, death following emergency operation and death from nonsurgical conditions. It is obvious that no detailed analysis need be made. The causes of death are listed in table 2.

To keep the record straight, a brief discussion must be made of some conditions, especially the malignant tumors, the septic abortions, the fatal peritoneal infections and the conditions causing deaths listed as medical.

Malignant Tumor: The vast majority of patients with malignant tumor were admitted just before death, for terminal care only. During this time carcinoma of the cervix was never operated on intentionally. In 2 of the 17 cases total hysterectomy was done under a mistaken diag-

TABLE 1.—*Deaths from Hysterectomy (Ten Years)*

	1930-1934	Mortality, Per Cent	1935-1939	Mortality Per Cent
Total abdominal hysterectomy	821	2.6	1,436	0.77
Subtotal abdominal hysterectomy	653	2.3	348	2.3
Vaginal hysterectomy	70	2.9	130	3.0

TABLE 2.—*Data in Group 1 (Malignant Tumors; Emergency Operations; Nonsurgical Conditions)*

Carcinoma of cervix	17	Medical causes	10
Carcinoma of fundus	7	Hemorrhage from tubal pregnancy	1
Carcinoma of ovary	14	Ruptured gallbladder	1
Septic abortion	16	Carcinoma of vulva, bowel, breasts and bladder, 1 each	4
Peritonitis	11		
Intestinal obstruction	3		

Total, 84 cases.

nosis and a carcinoma was found originating high in the cervix and involving the broad ligaments. One patient died of embolus and the other of shock and hemorrhage. All others were being treated or had been treated with radium and roentgen therapy.

Five patients with malignant tumor of the uterine fundus were admitted for terminal care. The other 2 were operated on; 1 died of embolus, and the other, who had a sarcoma, of hemorrhage and shock.

All carcinomas of the ovary were or had been operated on, at least for exploration and removal of a specimen for biopsy.

Septic Abortion: Treatment of septic abortion, which in the great majority of cases was self induced or criminally induced, was in all but 1 instance conservative. In 1 case the uterus was invaded for what was considered to be serious hemorrhage.

Peritonitis: All patients who died of peritonitis had frank peritonitis, pelvic abscess or a severe pelvic infection on admission to the hospital.

None of them had undergone an operation other than drainage of a localized accumulation of pus (usually by posterior colpotomy) except 1, a pregnant woman in whom peritonitis followed emergency appendectomy at term. At autopsy 2 other pelvic peritoneal infections were observed and were found to have been primarily appendical. The remaining 8 were, as had been thought before death, tubal in origin.

Any death following a pelvic infection for which through an error in diagnosis or judgment the patient was operated on has been included as a death due to an elective surgical procedure.

Nonoperative Deaths: For one reason or another an appreciable number of medical deaths occurred. Some of the patients had not yet come to operation, and some were former patients of the service who were admitted without a clear diagnosis before study in the hospital. The causes of death listed for this subgroup were asthma, terminal tuberculosis of the urinary or the genital tract, toxemia of pregnancy, pulmonary embolus without operation, influenza, septicemia from a pharyngeal infection, cardiac disease (1 case) and granulocytopenia possibly due to sulfanilamide (1 case).

The death by hemorrhage due to an ectopic pregnancy occurred on the elevator en route to the floor. In all cases of intestinal obstruction emergency operations were performed. None of the patients had, at least recently, been operated on in this hospital or elsewhere.

Group 2.—This group, of 63 cases, included all in which death followed an elective operation.

Of the 63 deaths in this group a more critical and detailed analysis was made. The patients, at least before operation, had been expected to get well.

A great many general statistics on average age, height-weight ratios, stay in the hospital before operation, blood counts, etc., are available and could be recorded, but it is thought that inclusion of too many tables, most of which have no bearing, makes for difficult reading; hence only items pertinent to the subject under discussion are included. In general the patients were the ordinary average type observed in a gynecologic service, the great majority being admitted to the hospital when in their late thirties or in the forties.

Especially in the private service, there is not an established practice of holding a patient in the hospital several days before operation unless there is evidence in the preliminary examination to indicate special investigation. No elective surgical operation is ever done on a patient with a hemoglobin level of less than 50 per cent.

The anesthetic used for these patients was (1) nitrogen monoxide, oxygen and ether or (2) avertin with amylene hydrate, nitrogen monoxide, oxygen and ether.

It is desired at once to point out one or two difficulties which were encountered. In some instances there was reasonable doubt of the exact cause of death. This was chiefly true, of course, of a few patients who did not come to autopsy. For example, the impression is gained that the diagnosis of "embolus" is an overworked one. Without autopsy, in 2 or 3 instances, by no reasonable stretch of the imagination could the explanation of death from embolus be sustained. It seemed more likely that in most of these cases (sometimes considerable evidence was obtained from the nurses' notes as well) peritonitis or some other infection was at least the primary cause of death, and this has been recorded. This may slightly exaggerate the number of the deaths from infection and diminish that of the deaths from embolus, but the latter are left as a clearcut group the cause of which was either proved by autopsy or indicated clearly by the manner of death.

TABLE 3.—*Data on Group 2 (Death from Elective Operation)*

		Autopsy Performed			Autopsy Performed
Peritonitis	22	10	Transfusion	2	2
Hemorrhage and shock	11	7	Spinal anesthesia	1	0
Embolus	10	5	Enteritis	1	1
Pneumonia	5	0	Duodenal fistula	1	0
Cardiac disease	5	1	Granulocytopenia	1	0
Intestinal obstruction	4	2			

Total, 63 cases.

Another difficulty in some cases, whether autopsy was performed or not, was in selecting a single primary cause of death from all the causes contributing thereto. Perhaps again an occasional arbitrary judgment was passed, due to assigning the most likely cause of death from a surgical point of view obtained after long study of, and consequent familiarity with, the patient's record.

The causes of death among the patients on whom elective operations were performed are listed in table 3.

Peritonitis: Twenty-two patients died of peritonitis. Of these, panhysterectomy was performed on 12, supracervical hysterectomy on 4, laparotomy of other types on 5 and a hysterosalpingographic procedure with iodized poppyseed oil on 1. Autopsies were obtained in 10 cases. In several others distinctive symptoms plus positive blood cultures made for a fairly definite diagnosis.

In 2 cases no definite factors contributing to peritonitis were made out. At once, in analyzing contributing causes in the remaining 20, there was encountered some overlapping, i. e., more than one contributing cause was present in some instances.

However, operation done in the presence of a temperature above 38 C. (100.4 F.), a leukocyte count above 8,000 per cubic millimeter or a sedimentation rate below sixty minutes (whether or not explained by the pelvic condition) heads the list of contributory causes. In all cases in which the pelvis was the site of infection pus was spilled. In the 4 cases in which the infection was not in the pelvis there was consistent failure to find out where it was before the operation. In the cases of pelvic infection operation was done through an error in diagnosis or judgment or both. The signs in most cases were thought to arise from degenerated fibroids, twisted cysts or fibroids. Occasional errors in judgment occurred in operations for known pelvic infection, due to inaccurate judgment of the extent or acuteness of the disease and of the condition of the patient. It may be said that in general such operations were done more frequently in the early half of the decade. More and more forcibly there has been driven home the lesson that a rapid sedimentation rate cannot be disregarded.

Difficult operations over two hours in duration or pelvic work combined with operation on the gallbladder or with hernia reduction, which in the final analysis is about the same thing, were next in prominence, contributing to peritonitis in 10 cases. Eight such operations, including the four combined procedures, were not associated with or difficult because of pelvic or other infection. Unusual obesity was present in 3 cases. In 1 case (operation was performed by one of the younger surgeons) insistence on doing panhysterectomy instead of supracervical amputation on a very obese woman who was a poor anesthetic risk probably prolonged the operating time in general. The greater number of deaths from panhysterectomy in this group does not mean that peritonitis is more common after this operation than after other types of hysterectomy. It is the hysterectomy of choice in this clinic, the supracervical procedure being done less often, as may be seen from table 1. It is only fair to say that the subtotal operation is usually performed on the patient who is considered susceptible to infection. This indicates that it is important to study many cases before conclusions are drawn.

Of interest are some of the predisposing causes to peritonitis. In these 22 operations the bladder was torn 3 times, the tear being a definite contribution to infection of the peritoneum in 2 instances. One panhysterectomy was performed (in a case of unsuspected incomplete abortion) in the mistaken belief that the uterus contained a fibroid. Peritonitis followed a hysterosalpingographic procedure done in an outside laboratory in 1 instance. In this series anemia was not a factor, preoperative correction of it when it existed having been thorough. Syphilis was not prominent in these patients, being present in only 2.

The factors contributing to peritonitis may be listed as follows:

Pelvic infection	6
Unknown infection	4
Long operation	6
Combined operation	4
Bladder torn	3
Incomplete abortion	1
Hysterosalpingography	1

Therefore, excluding the hysterosalpingographic procedure, twenty-four major factors operated in 20 cases to contribute to peritonitis.

Hemorrhage and Shock: All deaths from hemorrhage and shock occurred within a few hours of operation except 2. In 2 cases reoperation prolonged life to three and eight days, respectively, infection playing a part in the fatal result in both. Autopsy or reoperation confirmed the diagnosis in 9 of the 11 cases. I am of that school whose members believe that fatal shock seldom occurs during a pelvic operation unless there is hemorrhage; therefore, the two conditions are not separated.

Supracervical hysterectomy was performed on 7 of these patients. As in this clinic this type of hysterectomy is performed by most operators only in cases in which trouble is encountered, an idea of why hemorrhage occurred is at once gained. Three of the 7 patients should not have been operated on, as they had preoperative fever, leukocytosis and rapid sedimentation rates from pelvic infection either with or without fibroids. Three of the remaining 4 had large or difficult fibroids, one of which was described as fitting the pelvis like a cork in a bottle. The seventh death occurred by bleeding from a corpus luteum damaged at operation and unnoticed before closure.

Hemorrhage in the remaining 4 cases occurred as follows: (1) in a vaginal hysterectomy done by an occasional operator; (2) in a suspension operation with the point of bleeding never definitely found; (3) in an exploratory laparotomy on a large parasitic fibroid which was never delivered, and (4) in 1 uncomplicated panhysterectomy (the bleeding was postoperative, from the left ovarian pedicle).

In 2 cases failure to correct further an existing anemia could be criticized. Both patients, however, had been given repeated transfusions and were bleeding vaginally. Syphilis was not a prominent factor, being present in but 2 instances.

The factors contributing to hemorrhage and shock may be listed as follows:

Operation for pelvic infection	3
Large complicated myoma	4
Vaginal hysterectomy by occasional operator	1
None except technical	3

Embolus: A study of a group of 10 patients who died from embolus yields less information as to contributing factors than does any other group. Embolus is, of course, well known as a complication of pelvic operations as well as an occasional complication of any other operation, even the simplest, and once in a while it occurs without an operation. Pulmonary embolus (including the air embolus) was proved by autopsy in 5 of the 10 cases. In 4 it occurred after panhysterectomy, in 2 after supracervical hysterectomy, in 2 after vaginal hysterectomy and in 1 after a suspension operation. The air embolus occurred during the performance of Rubin's test with an antiquated air apparatus; the patient had small fibroids in the uterus. Curettage had not been done before injection of the air.

In this group there was no preoperative anemia and no positive serologic reaction for syphilis. In only 1 patient was the white blood cell count above 8,000 per cubic millimeter and the sedimentation rate increased; the increase was slight and was not explained by the pelvic condition. Five of the patients underwent operations lasting two hours or slightly more. Prolonged operation was the only more or less constant factor, but none of the procedures were particularly difficult. Therefore, there was no definite contributing cause to embolism in this group. Not routinely, but by most physicians, early activity of the patient is urged, and thyroid medication is used postoperatively to guard against stasis in the circulatory system.

Pneumonia: Five patients who died of pneumonia were anesthetized with nitrogen monoxide, with oxygen and ether or with ether given by the drop method. Three of the operations lasted longer than two hours. None of the patients were above 60 years of age. Two were obese; 2 had positive serologic reactions; 1 was hypertensive, and 1 had a rheumatic heart. The operations included 2 supracervical hysterectomies, 1 vaginal hysterectomy and 1 abdominal panhysterectomy. The deaths were all correlated with the time of year in which the operation was done. None occurred during the winter months, the latest taking place in October. It is perhaps noteworthy that since 1937 no deaths have occurred in the gynecologic service primarily from pneumonia. Perhaps chemotherapy and better general methods of treating this disease, as well as improved anesthetics, have a bearing on this fact. None of the patients had preoperative pulmonary abnormalities; 3 had rapid sedimentation rates not explained by the pelvic condition.

Cardiac Disease: The 5 patients who died of cardiac disease had preoperative diseases in abundance. Three were above 60 years of age. Two who died on being put into the Trendelenburg position were obese and had positive serologic reactions. One was severely diabetic and arteriosclerotic. All died at operation or shortly afterward except 1, who lived twenty-three days, moderate uremia and pelvic peritonitis con-

tributing to the ultimate fatality. Vaginal hysterectomy was performed on 2 of these patients; a mesenteric cyst was excised in 1, and 2 underwent exploratory operations, with subsequent hysterectomy contemplated.

Intestinal Obstruction: Obstruction followed panhysterectomy in 2 instances. One panhysterectomy was a long procedure combined with an operation on the gallbladder; the other was performed on a patient who had a positive serologic reaction for syphilis and an uncorrected low level of hemoglobin (45 per cent [Sahli]) before operation. Obstruction followed supracervical hysterectomy in 1 instance, the patient being a woman 67 years of age. The final patient was a young woman in whom obstruction followed a Baldy-Webster suspension. All were reoperated on except the one in whom obstruction followed the suspension operation. All died on the fifth postoperative day. There have been no primary intestinal obstructions listed as causes of death in the service since 1934. It is possible that some of these patients would have been saved had the Miller-Abbott tube been in use at that time.

Transfusion: There were 2 deaths from transfusion. One of these was due to proved faulty matching and the other was a delayed reaction occurring after three days, the reasons for which were less plain. Permission for autopsy was obtained in both instances.

Spinal Anesthesia: This type of anesthesia is not in common use in our service. One death occurred on the day of operation, after an easy vaginal hysterectomy. It was attributed to bulbar paralysis. Autopsy was not performed.

Enteritis, duodenal fistula and agranulocytopenia, which accounted for 1 death each, are not of statistical value. The patient who died of enteritis had undergone panhysterectomy. The duodenal fistula resulted from operation for an extremely severe pathologic condition of the gallbladder. The granulocytopenia followed an operation for repair only and was thought to be an influenzal type of infection.

Summary of Deaths Following Elective Operations.—Of the 63 cases in which the patients died after an elective operation, peritonitis was the primary cause of death in 30.5 per cent. Death from peritonitis frequently follows operation on a patient with preoperative fever, leukocytosis and particularly a rapid sedimentation rate. Many such patients get well, but some do not, as these figures reveal. Except in rare instances of larger fibroids, a rapid sedimentation rate means accompanying pelvic infection, and immediate operation should no more be done for this combination than for pelvic infection alone. Attention is also called to the occasional rapid sedimentation rate unexplained by the pelvic condition and to the necessity for more preoperative investigation under such circumstances. Peritonitis is apparently more frequent in

patients who have been subjected to long or combined operations, even though the operation is not associated with any particular difficulty.

Similarly, death from hemorrhage and shock is frequently associated with operation done in the presence of fever, leukocytosis or a rapid sedimentation rate. In addition, review of the records shows the necessity with large tumors of taking plenty of room and of careful, well organized attack on the blood supply. With the mass ties still considered necessary in pelvic operations, transfixion and double tying of pedicles are indicated, certainly in the hands of the beginner.

No worth while contributory facts as to embolism can be deduced from these cases, but it is pointed out that in half of them the operation, though not difficult, lasted more than two hours.

It is thought that because of improved anesthetics, improved methods of administration of anesthetics and better methods of treating pneumonia this postoperative complication has been less often fatal during the last five years.

In this clinic no deaths from postoperative obstruction were recorded during the last half of the decade under consideration. There is an impression that this complication is becoming less frequent; certainly since the advent of the Miller-Abbott tube it has been less feared.

Syphilis, except in patients with cardiac disease, was not a prominent cause of death from gynecologic procedures.

On the whole, there is no criticism in this clinic of the correction of preoperative anemia.

TREATMENT OF INTUSSUSCEPTION

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During the years from 1920 to 1939, inclusive, 133 patients were admitted to the Children's Memorial Hospital with the diagnosis of intussusception. In every instance the diagnosis was proved either at operation or necropsy, with 15 exceptions, which will be discussed further. Tables 1, 2, 3 and 4 are self explanatory and show some of the pertinent facts concerning the entire group.

Of significance is the fact that enemas given to 64 of the 133 patients failed to produce reduction in all except 11. This is in contrast to Hipsley's [1] results. He procured a reduction in 60 per cent of his patients by this method with only one perforation of the bowel in more than 300 patients. The chief criticism of the method used by Hipsley is that one cannot be certain that reduction of the intussusception has occurred following the enema. Then, too, this method would seem to be useless when the intussusception is above the ileocecal valve.

Various operative procedures were used to produce reduction in the patients whose cases are reported here. In all the patients operated on an attempt was made to procure reduction of the intussusception by the Farr [2] inflation method and manipulation. In the Farr procedure a rubber catheter with a blood pressure bulb attached is inserted into the rectum before administration of the anesthetic is started. After the abdomen is opened and the intussusception is located, the bowel is inflated through the rectal catheter under the guidance of the operator's hand, and manipulation is started. Inflation alone usually causes a partial reduction and has effected complete reduction in some instances. A reduction by inflation and manipulation was successful for 92 (83 per cent) of the 100 patients on whom the method was employed. When this method failed, other procedures to be described were used. Two patients were operated on by the method which Montgomery and Mussil [3] established on an experimental basis. In this operation the unreducible bowel is left in

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From the surgical service of Dr. A. H. Montgomery at the Children's Memorial Hospital.

1. Hipsley, R. L.: Intussusception, J. A. M. A. **106**:137 (Jan. 11) 1936.

2. Farr, C. E.: A Reduction of Colonic Intussusception by Air Inflation, Ann. Surg. **84**:588-590 (Oct.) 1926.

3. Montgomery, A. H., and Mussil, J. J.: The Treatment of Irreducible Intussusceptions in Children, Surg., Gynec. & Obst. **51**:415-419 (Sept.) 1930.

place, and the intussuscipiens is sutured to the intussusceptum; after this a side to side anastomosis of the bowel is made. One of the 2 patients treated by this method died. In 4 other patients in whom reduction was unsuccessful only a side to side anastomosis was performed, and 3 died. The affected bowel was excised in 4 patients. Three of these had a lateral anastomosis; 1 had an end to end anastomosis, and all died. In 2 patients the bowel was successfully reduced, but its viability was questionable, so a lateral anastomosis was made; 1 lived, and 1 died. One patient on whom a lateral anastomosis was made because of an ulcer of the ileum survived, but another patient who had the same operation for a narrowing of the bowel after Meckel's diverticulum was excised died.

TABLE 1.—*Summary of Results in Cases of Intussusception*

Dates	Patients	Boys	Girls	Average Time in Hospital, Days	Patients Given Preoperative Enema	Cures by Preoperative Enema	Recurrences After Operation	Deaths
1920 to 1930.....	54	36 (67%)	18 (33%)	7¼	29 (54%)	6	None	22 (41%)
1930 to 1940.....	79	51 (64%)	28 (36%)	10½	35 (44%)	5	2 (2.5%)	17 (22%)
Total for 20 years....	133	65%	35%	8.9	64 (48%)	11 (8.3%)	2 (1.5%)	39 (29%)

TABLE 2.—*Ages of Patients in Whom Reduction Was Successful*

Dates	Under 1 Yr.	1 to 2 Yr.	2 to 3 Yr.	3 to 4 Yr.	4 to 5 Yr.	5 to 6 Yr.	6 to 7 Yr.	7 to 8 Yr.	8 to 9 Yr.
1920 to 1930.....	41	6	2	3	0	2	0	0	0
1930 to 1940.....	51	18	5	2	0	0	1	0	2
Total for 20 years	92	24	7	5	0	2	1	0	2

Ileostomy alone was performed on 3 patients, and they died. In 1 patient the intussuscipiens was incised and the bowel then sutured longitudinally; death followed. Of these 18 patients ~~in whom~~ some operative procedure was performed on the bowel itself, 14 (78 per cent) died.

Spontaneous reduction occurred in 1 patient during operation. In 4, the bowel was found reduced at operation.

Eighteen patients were not operated on. In 11 of these reduction was obtained by an enema, and in 3 reduction was thought to have come about spontaneously. Three died. Operation was prohibited by the parents of 2 patients; 1 of these recovered, and the other died at home.

During the decade from 1920 to 1930 there was a total of 54 patients admitted, with 22 deaths (41 per cent); in the following decade from 1930 to 1940 there were 79 admitted and 17 deaths (22 per cent). This shows the decrease in mortality which results from experience; some of the surgeons were in attendance the entire twenty years.

In 2 recently admitted patients, reduction could not be accomplished by the method of rectal inflation and bowel manipulation. Brief histories of these 2 cases are now presented.

REPORT OF CASES

CASE 1.—A Polish boy aged 4 months was brought to the Children's Memorial Hospital Nov. 11, 1939 with a history of vomiting and bloody stools during the preceding twenty-four hours. The child appeared toxic. A cylindric mass was palpable beneath the left rectus muscle. Rectal examination revealed a cervix-like mass and blood on the examiner's finger. A laparotomy was performed, and an ileocecal intussusception was found extending from the lower part of the ileum to

TABLE 3.—*Time of Operation with Reference to Onset of Illness*

Dates	Cases	Within First 12 Hr.	12 to 24 Hr.	24 to 48 Hr.	48 to 72 Hr.	Over 72 Hr.
1920 to 1930	46	6 (13%)	5 (11%)	10 (22%)	9 (19%)	16 (35%)
1930 to 1940	69	19 (27%)	4 (6%)	18 (26%)	13 (19%)	15 (22%)
Total for 20 years	115	25 (22%)	9 (8%)	28 (24%)	22 (19%)	31 (27%)

TABLE 4.—*Preoperative Findings*

Dates	Patients	Patients with Preoperative Vomiting	Patients with Preoperative Abdominal Mass	Patients from Whom Rectal Blood Was Obtained on Examiner's Finger
1920 to 1930	54	53 (98%)	38 (70%)	19 (35%)
1930 to 1940	79	70 (88%)	58 (73%)	45 (58%)
Total for 20 years	133	123 (92%)	96 (72%)	64 (48%)

the lower part of the rectum. Inflation of the bowel through a rectal catheter and manipulation failed to disengage the proximal 2 inches (5 cm.) of the invaginated bowel. About 10 cc. of glycerin was then injected with a syringe between the intussuscipiens and the intussusceptum. The neck of the intussuscipiens was grasped to retain the glycerin, and the right forefinger was placed into the neck and moved around to distribute this lubricant. Reduction was thus accomplished, and recovery was uneventful.

CASE 2.—A white boy aged 7 months was admitted March 30, 1940 with a history of vomiting of eighteen hours' duration. A sausage-shaped mass about 3 inches (7.5 cm.) long was palpable in the left side of the abdomen. During rectal examination blood was revealed on the examiner's finger. At laparotomy an ileocecal intussusception about 10 inches (2.5 cm.) long was found that could not be reduced by rectal inflation and manipulation. Glycerin was injected as in the preceding case and reduction accomplished. Recovery was uneventful.

The high mortality rate of this disease relates especially to the group of cases in which reduction is impossible. A method was sought which

would increase the number of cases in which reduction could be obtained by manual methods.

On viewing an intussusception before reduction one might believe that there was a narrow ring at the neck of the intussuscipiens and that this prevented reduction. After reduction, however, no narrow ring is seen at this site. There is, however, some thickening of the bowel wall, in most instances due to edema. A finger can be introduced into the neck and readily swept from one mesenteric border to the other. Hence, narrowness of the ring does not seem to be the chief cause for the failure of reduction; in many instances the reason seems to be that the bowel serosa is inflamed and roughened. This condition causes the two opposing bowel layers to adhere to one another, with friction, and thus prevents reduction. It was thought probable that a lubricant introduced between the intussuscipiens and the intussusceptum would obviate this difficulty of reduction. Glycerin was chosen as the substance least likely to damage the bowel. Furthermore, glycerin is hygroscopic and probably has some tendency to remove the edematous fluid from the bowel wall, thereby assisting in reduction.

Glycerin was successfully employed in the aforementioned 2 patients in whom reduction was impossible. Five to 10 cc. of glycerin was injected between the intussuscipiens and intussusceptum with a 2 cc. syringe. On removal of the syringe the neck was grasped with the thumb and forefinger of the left hand, while the forefinger of the right hand was introduced through the neck and swept the glycerin around from one mesenteric border to the other as further attempts were made at disinvagination. Finally complete reduction was obtained. After reduction was gained, as much as possible of the glycerin was removed with a sponge.

SUMMARY

In the years from 1920 to 1940, 133 patients were admitted to the Children's Memorial Hospital, Chicago, with a diagnosis of intussusception. The mortality rate for those admitted from 1920 to 1930 was 41 per cent; the mortality rate from 1930 to 1940 was 22 per cent. In 2 patients with irreducible intussusceptions glycerin was injected between the intussuscipiens and the intussusceptum and successful reductions accomplished.

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RELATION OF SPLENIC EXTRACT TO ETIOLOGY OF ESSENTIAL THROMBOPENIA

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In 1938 Troland and Lee [1] reported 3 cases of thrombopenic purpura in which they were able to prepare from the patient's spleen an extract which had platelet-reducing properties when injected into rabbits. In all 3 cases splenectomy resulted in amelioration of symptoms. The spleens were small, the largest weighing 136 Gm. Similar work had been reported by Torrioli and his associates,[2] beginning in 1933; attempts at confirmation have thus far been inconclusive.[3] Following the methods of Troland and Lee, we attempted to confirm their results. Our first extract was prepared from a spleen removed at another institution. We were able to secure three more spleens, one from the surgical service of the Flower and Fifth Avenue hospitals.

METHODS

Extraction.—Splenic tissue was chopped fine and placed in five times its volume of reagent acetone (chemically pure) immediately after removal. The first extract (to be known as extract A, fractions as A-1, etc.) was prepared after six months' ripening; the length of ripening and case histories for extracts B and C are unknown, the spleens from which they were prepared having been sent to us as a control on experiments being done simultaneously at another institution. The period of ripening of extract D-1 was one week after splenectomy; that of extract D-2, two weeks; that of extract D-3, three weeks, and that of extract D-4, three months. Except when otherwise noted, the method of extraction was the same in all instances. Sterile equipment was employed throughout.

A quantity of supernatant acetone was removed with a pipet from the splenic tissue below and filtered into a glass vessel with a side arm through sterile hard

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1. Troland, C. E., and Lee, F. C.: Thrombocytopen, J. A. M. A. **111**:221 (July 16) 1938.

2. Torrioli, M., and Puddu, V.: Recent Studies on the Pathogenesis of Werlhof's Disease, J. A. M. A. **111**:1455 (Oct. 15) 1938.

3. Hobson, F. C. G., and Witts, L. J.: Platelet Reducing Extracts of the Spleen, Brit. M. J. **1**:50 (Jan. 13)1940. Major, R. H., and Weber C. J.: Is There a Platelet Reducing Substance in the Spleen of Thrombocytopenic Purpura? J. Lab. & Clin. Med. **25**:10 (Oct.) 1939.

filter paper. Distillation was carried out by using negative pressure from a water aspirator, the system being air tight. The temperature was kept between 25 and 29 C.

Distillation was discontinued when constant volume was maintained and the residue was orange-brown and syrupy. The residue was then dissolved in sterile distilled water sufficient to equal the predistillation volume and was stored in a vaccine bottle in a refrigerator.

Fraction A-9 was prepared by allowing the acetone to evaporate in open air for twenty-four hours. The residue was treated as usual. Fraction D-3 was prepared by bubbling air through a fine capillary tube placed in the acetone solution; the residue was treated according to routine.

Several fractions were tested qualitatively for acetone by the nitroprusside method; all samples gave a strongly positive reaction. Since acetone was present in all samples tested, it could not account for the low counts obtained for rabbits 1 and 3.

Fraction A-8 was tested by the bacteriology department to check on our technic; no growth in pour plates or in broth cultures was reported.

Standardization.—After observation the apparent effectiveness of our extract in rabbits 1 and 3, we attempted to standardize its potency. We used white mice weighing 6 to 8 Gm. Intraperitoneal injections of as much as 1 cc. were not lethal; the animals were killed after twenty-four hours, and no hemorrhagic phenomena were seen at autopsy.

Animals.—Rabbits weighing 4 to 8 pounds (1.8 to 3.6 Kg.) were used throughout the experiments. From rabbits 5, 6, 9, 10 and 17 biopsy specimens were taken of the femoral and costal marrow and of the spleen. Four to six weeks was allowed for recovery from the effects of operation. Histologic examination of the same tissues at the end of our experiments showed no significant changes. Slides of spleen and bone marrow from rabbits 1 and 3 were also normal.

Sources of Extracts.—The A series of extracts was prepared from a spleen weighing 136 Gm., removed from a 33 year old woman in whose case a diagnosis of essential thrombopenic purpura had been established clinically at another institution. We know nothing about the spleens from which extracts B and C were prepared, these having been sent to us as controls only; they may have been removed for another reason.

The complete history of the patient from whose spleen the D series was prepared is available and is presented in abstract form. E. C., a girl aged 8 years, in 1936 reported to the outpatient department with a history of spontaneous petechiae and ecchymoses beginning at the age of 2 years. At the first visit the platelet count was low and the tourniquet test gave a negative result. During the next four years the patient was seen several times; thrombopenia, with a platelet count of about 100,000 per cubic millimeter of blood, was consistently noted; clot retraction became delayed, and the Hess test gave a positive result. Remissions were noted by the family. At different times hemorrhagic phenomena were found in the skin, conjunctivas, oral mucosa and tympanic membrane. The onset of symptoms often coincided with the onset of an infection of the upper respiratory tract, which was the chief complaint on four admissions to the hospital. In view of the (at times) prolonged bleeding time (up to twenty-one and one-half minutes) and poor clot retraction, tonsillectomy was refused by the department of otolaryngology. In April 1940 she was admitted with widespread purpura and tonsillitis; the latter cleared up under treatment. The platelet count was 30,000

per cubic millimeter; there was no anemia; the bleeding and coagulation times were normal; the Hess test gave a positive result, and the bone marrow was normal except for an increase of megakaryocytes. It was decided that she had chronic recurring essential thrombopenic purpura and that in view of the widespread distribution of the purpura a more serious accident could occur. The platelet count was repeatedly below 50,000 per cubic millimeters; forty-five minutes before operation a count of 45,000 was recorded. On April 14, 1940, splenectomy was performed; the spleen weighed 96 Gm. and was microscopically "compatible with thrombopenic purpura." Immediately after ligation of the pedicle the platelet count was 100,000 per cubic millimeter; in twenty-four hours it was 172,500; daily counts thereafter were 197,500; 320,000; 530,000; 615,000; 560,000; 500,000; 510,000, and, in two weeks, 700,000. After discharge she returned to the clinic on June 26 with a recurrence of the purpura despite a normal platelet level. On October 9 she returned for follow-up examination. The history revealed the occurrence of the menarche, with normal menses in August and September, of average quantity and duration. During July the purpura had cleared up. The platelets numbered 360,000 per cubic millimeters; the bleeding, clotting and clot retraction times were not prolonged, and the Hess test gave a negative result. By November 7, a relapse occurred, many ecchymoses and petechiae being present; the coagulation time was seven and one-half minutes, and the bleeding time, nine minutes; the platelets numbered 20,000 per cubic millimeter, and the tourniquet test gave a positive result. A normal menstrual period was reported for October. On Jan. 22, 1941, E. C. reported for follow-up examination; normal menses were recorded for November, December and January. The petechiae and ecchymoses noted on the previous visit faded shortly thereafter and have not recurred. No time has been lost from school to date, and only one episode of disease of the upper respiratory tract has occurred. Physical examination revealed the girl to be well nourished and well developed. She showed no hemorrhagic phenomena. The tourniquet test gave a negative result; the bleeding time was three minutes and five seconds, and the platelets numbered 180,000 per cubic millimeter. We believe that the evidence to date confirms the clinical diagnosis of essential thrombopenic purpura.

During hospitalization the patient was tested with intracutaneous injections of an extract of her own and of one other spleen (extract A preoperatively). She did not react.

All platelet counts reported in this paper were determined according to the method of Rees and Ecker.[4] Our technic was checked several times by technicians on the hospital staff.

EXPERIMENTAL STUDIES

After the preinjection level of the blood platelets had been established the extract was injected intravenously into rabbits. As can be seen in the accompanying table, counts were done at varying intervals. An analysis of the results shows that rabbits 1 and 3 gave markedly positive reactions, registering definite and large decrease in the platelet level; the transitory drop was accompanied with an increased bleeding time for rabbit 1 only. It was decided to call the extract potent if the platelet level fell to the neighborhood of the critical level of Duke, 35,000 per cubic millimeter.[5] In none of the other experiments was there a drop which

4. Rees, H. M., and Ecker, E. E.: Improved Method for Counting Blood Platelets, J. A. M. A. **80**:621 (March 3) 1923.

5. Duke, W. W.: The Relation of Blood Platelets to Hemorrhagic Disease, J. A. M. A. **55**:1185 (Oct. 1) 1910.

Data on Experiments with Splenic Extracts

Rabbit	1	2	3	4	4	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Preinjection level	415	455	445	570	590	770	410	390	475	495	415	420	535	640	460	550	610	415	530
Extract: Number	A-1	A-2*	A-3	B	C	A-4	A-5	A-6	A-7	A-7	A-8	A-8	A-8	A-8	A-9	D-1	D-2	D-3	D-4
Amount, cc.	1.8	1.7	7.5	5	5	3.5	3	0.8	7.5	2.5	2	2	2	2	2	5	8.25	7.8	5
Platelet counts† and time elapsed	7 hr. 581‡	4 hr. 350	6 hr. 95	6 hr. 495	7 hr. 505	6 hr. 495	4 hr. 475	4 hr. 640	4 hr. 575	3 hr. 275	4 hr. 490	4 hr. 540	4 hr. 505	4 hr. 615	3 hr. 332	4 hr. 552	4 hr. 615	4 hr. 390	5 hr. 500
	26 hr. 240	6 hr. 395	26 hr. 425	....	....	....	7 hr. 325 B.T. 9′	7 hr. 670	7 hr. 502	6 hr. 450	7 hr. 435	7 hr. 510	7 hr. 730	7 hr. 445	6 hr. 625	7 hr. 470	7 hr. 660	10 hr. 530	13 hr. 480
	2 days 100	26 hr. 365	5 days 610	....	....	....	11 hr. 350 B.T. 1½′	28 hr. 490	10 hr. 367	11 hr. 500	12 hr. 505	12 hr. 475	12 hr. 605	12 hr. 500	24 hr. 380	12 hr. 505	11 hr. 550	24 hr. 505	
	3 days 185	4 days 375	8 days 405	....	....	....	24 hr. 425	3 days 805	24 hr. 437	24 hr. 590	24 hr. 375	24 hr. 405	24 hr. 450	24 hr. 550	....	24 hr. 450	24 hr. 570	2 days 450	
												Simultaneous determinations							
	6 days 305	A-2‡ 3 cc. 6 hr. 645	....	....	....	....	2 days 530	4 days 715	2 days 625	2 days 505	....	....	....	....	....	2 days 505	2 days 490		
									Simultaneous determinations										
	7 days 385	29 hr. 600	....	....	....	....	3 days 855	5 days clumps 440±?	....	....	....	....	....	....	....	8 days 560			
	8 days 440	3 days 610	....	....	....	....	4 days 625	6 days 575	....	....	....	....	....	....	....	17 days 490			
	13 days 780	4 days 510	....	....	....	....	6 days 705												
	21 days 650	8 days 430	....	....	....	....	7 days 745												
	35 days 555	22 days 410	....	....	....	....	8 days 620												
							9 days 560												

* Counts in thousands per cubic millimeter.
† Bleeding time 11 minutes; bleeding time determined with each count, and all were in normal range.
‡ Extract frozen and thawed at room temperature.

even approximated this arbitrary standard. In only 1 other instance was the bleeding time increased above normal (rabbit 5, nine minutes); the lowest platelet count in this instance was 325,000.

Rabbits 7 and 8 were used to control the dosage; rabbit 8 (dose, 2.5 cc.) registered a greater drop than rabbit 7 (dose, 7.5 cc.). This decrease still did not approach the level set for potency of the extract. Extract A-8 was injected into 4 rabbits so that simultaneous determinations could be made; these animals showed practically no diminution of platelets.

We are not prepared to speculate on the instance in which elevation of the count was noted. We cannot explain the paradoxically excellent results with rabbits 1 and 3.

SUMMARY

Seventeen experiments were performed with extracts of spleens removed in cases of idiopathic purpura haemorrhagica of Werlhof. Two of these (experiments 1 and 3) gave positive results. The results of the rest were, in our opinion, negative, although in some there were slight transitory drops. In several instances the counts rose rather than dropped. One patient was given a cutaneous test with an extract of her own and one other spleen and was found not to react. In those rabbits in which thrombopenia was produced no spontaneous hemorrhagic phenomena appeared; in only 2 cases was the bleeding time prolonged. Two experiments were done with extracts made from spleens removed for an unknown cause; these extracts likewise showed no potency.

CONCLUSION

We were unable to demonstrate consistently the presence of a platelet-reducing substance in acetone extracts of spleens from patients with thrombopenic purpura of Werlhof or in extracts from 2 spleens of unknown pathologic condition when injected into rabbits.

NERVES IN THE VERTEBRAL CANAL

THEIR RELATION TO THE SYMPATHETIC INNERVATION OF THE UPPER EXTREMITIES

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According to current accounts of the nerves in the vertebral canal, based mainly on the work of von Luschka (1850) [1] and Rüdinger (1863),[2] a recurrent or meningeal nerve arises from the communicating ramus of every spinal nerve and enters the vertebral canal through the corresponding intervertebral foramen. Within the vertebral canal these nerves bifurcate, sending a short division cephalad and another caudad. These divisions constitute a longitudinal strand of nerve fibers, the sinuvertebral nerve, located in the lateral region of the floor of the canal. Branches arising from the sinuvertebral nerve convey fibers to the meninges, to the blood vessels within the canal and to the membranes enveloping the spinal nerve roots.

Certain clinical observations reported by Simpson, Brown and Adson (1930),[3] White (1933),[4] Telford (1934) [5] and others support the assumption that in certain cases some sympathetic fibers in the upper extremity remain functionally intact following extirpation of the inferior cervical and upper two or three thoracic segments of the sympathetic trunk, an operation which cannot be carried out without interrupting all known pathways through which sympathetic nerve fibers enter the brachial plexus. The present investigation has been undertaken to determine the distribution of the sympathetic components of the nerves within the vertebral canal more accurately and to test the hypothesis that sympathetic nerve fibers which enter the vertebral canal

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2. Rüdinger, N.: Ueber die Verbreitung des Sympathicus in der animalen Röhre, dem Rückenmark und Gehirn, Munich, J. J. Lentner, 1863.

3. Simpson, S. L.; Brown, G. E., and Adson, A. W.: Observations on the Etiological Mechanism in Raynaud's Disease, Proc. Staff Meet., Mayo Clin. **5**:295-298, 1930.

4. White, J. C.: Progress in Surgery of the Sympathetic Nervous System in 1932, New England J. Med. **209**:843-850, 1933.

5. Telford, E. D.: Sympathectomy: A Review of One Hundred Operations, Lancet **1**:444-446, 1934.

at lower levels emerge through lower cervical and upper thoracic intervertebral foramens and join the nerves which innervate the upper extremity.

MATERIALS AND METHODS

The material used in the present study was obtained from normal and experimental animals (cats) and a human fetus at full term. The preparations of normal material consisted mainly of transverse sections of the decalcified vertebral column, including the spinal cord and meninges. In a series of normal young cats and a full term human fetus, the vertebral column with the contents of the vertebral canal was dissected out from the level of the eighth cervical to that of the tenth thoracic nerve, fixed in Bodian's [5a] solution no. 2, to which 5 Gm. of chloral hydrate per hundred cubic centimeters had been added, and then placed in Schridde's solution long enough to insure complete decalcification of the vertebrae. Paraffin sections of this material were impregnated with strong protein silver and toned with gold chloride.

Cats of another series were subjected to an operation in which the inferior cervical ganglion and the first, second and third thoracic segments of the sympathetic trunk were removed unilaterally and several of the upper thoracic spinal nerves on the same side were sectioned within the vertebral canal. The animals were killed four weeks after the operation. Then the contents of the intervertebral foramens on the side of the operation, through which the eighth cervical and the first and second thoracic nerves emerge, including the tissues connecting the vascular plexuses in the vertebral canal with these nerves, were carefully dissected out and prepared by the pyridine-silver technic. This material was sectioned serially, some of it transversely and some longitudinally.

Cats of a third series were subjected to unilateral extirpation of the inferior cervical and upper six thoracic sympathetic ganglions with the intervening portions of the sympathetic trunk. When these animals were killed, four weeks after the operation, all the segments of the vertebral column affected by the operation were dissected out, with the spinal cord intact, fixed, decalcified, sectioned and stained by the same methods as the material from the other animals.

ANATOMIC FINDINGS

In the sections of the material obtained from the animals not subjected to operation, bundles of nerve fibers arranged longitudinally were observed ventral to the longitudinal vertebral venous sinus and between it and the periosteum of the vertebrae. These bundles comprised both myelinated and unmyelinated fibers, but the unmyelinated always outnumbered the myelinated ones. They occupied approximately symmetric positions in either side of the vertebral canal and were accompanied by arteries. They maintained fairly constant positions between the periosteum and the venous sinuses throughout the length of the portion of the vertebral canal which was included in the serial sections (fig. 1). These nerves gave rise to branches, not all of which contained myelinated fibers. Some of the smaller ones were accom-

5a. Bodian, D.: Staining of Paraffin Sections of Nervous Tissues with Activated Protargol: Role of Fixatives, Anat. Rec. **69**:153-162, 1937.

panied by arteries and eventually entered the bony substance of the vertebrae; others extended outward in the intervertebral foramens in the connective tissue ventral to the spinal nerves. Every spinal nerve in the segments studied was joined by such a branch, which extended dorsalward through the longitudinal vertebral venous sinus and assumed a position in proximity to the more anterior motor rootlets of the spinal nerve which it accompanied outward in the intervertebral foramen (fig. 2). Some branches entered the vertebrae, but none were observed which crossed the medial plane.

Bundles of unmyelinated nerve fibers also were present in the dorsal region of the vertebral canal. They lay between the periosteum of the lamina of the vertebra and the posterior internal vertebral venous plexus.

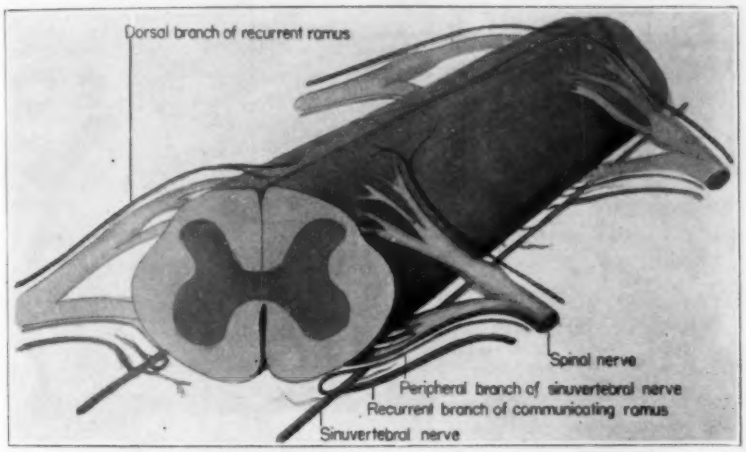

Fig. 1.—Nerves in the vertebral canal.

These bundles were small and did not maintain constant positions throughout the length of the canal. Most of them penetrated the bone of the vertebrae, but some pierced the ligamenta flava and extended outward between the arches of the vertebrae. Others extended into the intervertebral foramens in the connective tissue dorsal to the spinal nerves. Connections between the nerves lying ventral to the longitudinal vertebral venous sinus and those located dorsal to the internal vertebral plexus could not be observed.

In preparations of the material obtained from the human fetus, the arrangement of the recurrent rami and the nerves in the vertebral canal conformed in all essential respects to the pattern observed in the cat, but the nerves were relatively larger. The greater abundance of nerve components in the human vertebral canal is probably correlated with the greater complexity of the blood vessels.

In sections of the material taken from the animals which had been subjected to the operation involving removal of the sympathetic trunk from the inferior cervical to the seventh thoracic ganglion, the nerves lying ventral to the longitudinal vertebral venous sinus were present throughout the segments in question on the side on which operation had been performed as well as on the other. In the upper segments most of the smaller bundles of fibers had undergone degeneration on the operative side. Only the larger bundle persisted and some of its constituent fibers had degenerated. Some intact fibers deviated from this nerve and extended outward in the intervertebral foramens, close

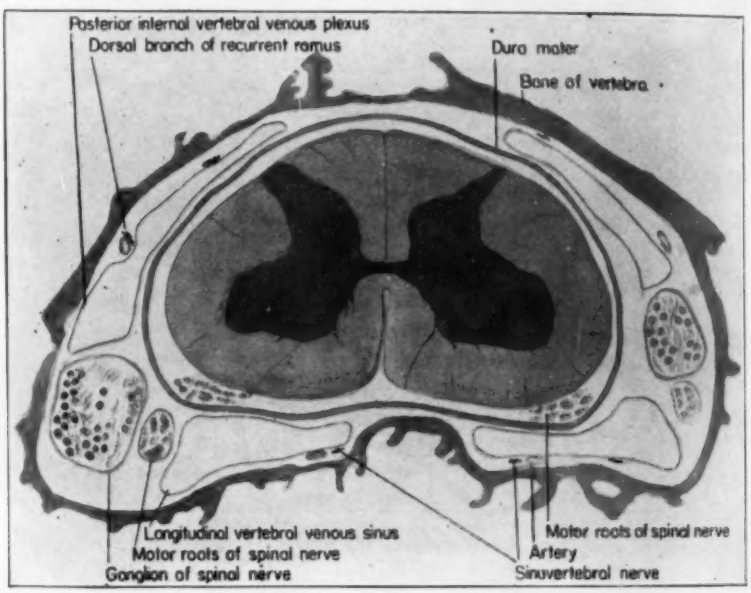

Fig. 2.—Cross section of vertebra.

to the fibers of the spinal nerve roots. In the upper segments studied, on the operative side no intact fibers could be observed in the dorsal region of the spinal canal between the periosteum and the posterior internal vertebral venous plexus.

In all sections of the tissue taken from the intervertebral canals of the animals in which the inferior cervical and the first, second and third thoracic ganglions and the intervening portions of the sympathetic trunk had been removed and the upper thoracic spinal nerve roots divided, bundles of intact unmyelinated fibers were observed lying parallel to the spinal nerves. In some cases, these bundles appeared to be inclosed in the fibrous sheath of the spinal nerve. They usually

included a few myelinated fibers. In the segments in which the spinal nerve fibers had undergone degeneration owing to section of the nerve roots within the vertebral canal, some of the myelinated fibers in the bundles in question, like the unmyelinated ones, had not been affected. The former probably were axons of the spinal ganglion cells located distal to the level at which the nerve roots were divided. The latter undoubtedly were sympathetic fibers which deviated from the sinuvertebral nerve and entered the intervertebral foramens to join the efferent roots of the spinal nerves. A pathway was thus demonstrated through which sympathetic fibers arising at lower levels might join the upper thoracic and lower cervical nerves and take part in the sympathetic innervation of the upper extremity.

CONCLUSIONS AND SUMMARY

The data obtained in the present investigation support the assumption that most of the constituent fibers of the recurrent branches of the communicating rami, but not all of them, terminate in relation to the blood vessels and the membranes within the vertebral canal. Some penetrate the bone of the vertebrae; some apparently join ventral spinal nerve roots at higher levels than the foramens through which they enter the vertebral canal. The unmyelinated fibers which extend outward in the intervertebral foramens along the ventral spinal nerve roots are undoubtedly components of recurrent rami which enter the vertebral canal at lower levels. The presence of such fibers in preparations of the material taken from the lower cervical and upper thoracic intervertebral foramens in animals from which the sympathetic trunk had been removed on the same side from the lower cervical to the seventh thoracic segment, inclusive, indicates that some sympathetic fibers ascend in the vertebral canal through six or more segments, at least in the upper thoracic region.

The unmyelinated fibers in the nerves in the dorsal region of the vertebral canal, like most of those in the nerves in the ventral region, are obviously derived from the sympathetic trunk ganglions located at the corresponding levels, since they have undergone degeneration in the material taken from the animals which had been subjected to extirpation of the ganglions of the sympathetic trunks in the same segments. These fibers undoubtedly innervate blood vessels in the vertebral canal, including those in the sheaths of the spinal nerve roots in the intervertebral foramens.

The presence in the vertebral canal of sympathetic fibers which arise at lower levels and emerge in the intervertebral foramens in the upper thoracic and lower cervical segments may be correlated with White's

finding, reported by Smithwick (1936),[6] that complete sympathetic denervation of the upper extremity in the monkey, by section of the anterior roots of the thoracic nerves, requires section of all the roots down as far as the twelfth thoracic segment. It also affords an explanation of the failure in some cases to bring about complete sympathetic denervation of the upper extremity by extirpation of the inferior cervical and upper two or three thoracic segments of the sympathetic trunk. Kirgis (1941)[7] demonstrated with human cadavers that in a large percentage of cases the third thoracic nerve gives rise to a slender ramus which joins the second thoracic nerve near the junction of the latter with its communicating ramus. This ramus, which includes a large number of unmyelinated fibers, and the intrathoracic ramus of the second thoracic nerve which joins the first (which, as demonstrated by Kuntz [1927],[8] also includes many unmyelinated fibers) afford a pathway through which sympathetic fibers arising in the third or lower thoracic ganglions of the sympathetic trunk may enter the upper extremity. In the absence of intact rami of this kind, sympathetic fibers which remain intact in the upper extremity after the usual operation for sympathetic denervation probably are fibers which arise at lower levels, ascend in the vertebral canal and join the nerves of the upper extremity through the intervertebral foramens in the upper thoracic and lower cervical segments. In certain cases, complete sympathetic denervation of the upper extremity probably cannot be accomplished without interruption of these fibers.

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TRICHOMONAS INFECTION OF THE MALE GENITOURINARY TRACT

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Trichomonas infection of the male genitourinary tract may not always be the harmless disease it has generally been considered. Standard textbooks have not contained adequate descriptions of this disease in men because relatively few cases have been reported. The literature has contained some excellent contributions on the subject, but as yet much of the work has been controversial.

The diagnosis and treatment of a disease are always of prime importance. In this article the clinical and laboratory diagnoses are given in detail. A new method of treatment for Trichomonas infection in men is presented, which may prove of value for certain aspects of the infection in women.

INCIDENCE

Trichomonas vaginalis was first described by Donné in 1836, but the potential pathologic manifestations were not appreciated until nearly the turn of the century. The first case involving the genitourinary tract of a man was described by Minura in 1894. Up to 1938 Thompson found 104 recorded cases and added 1 case of his own. In 1935 Karnaky reported 38 cases and Anthony 1 case. We do not understand just how many additional new cases Riba and Harrison were reporting in their last paper. We add 1 case of our own, making a total of 145 cases to date, exclusive of Riba and Harrison's report.

Women are admitted to have Trichomonas infection of the genitourinary tract much more frequently than men. For example, Stuhler stated that from 40 to 60 per cent of adult women have T. vaginalis infection of the genitourinary tract.

Nitschke gave excellent anatomic, physiologic, biologic and pathologic reasons for the difference of incidence in the two sexes. However, we are not convinced that Trichomonas infection of the genitourinary tract commonly occurs by contamination with Trichomonas hominis from the anus.

On the incidence in men there have been two widely contrasting types of reports. Stuhler found that in 32,000 examinations of prostatic

secretion T. vaginalis was found in only 16 or once in every 2,000 examinations. Riba examined 3,000 specimens of prostatic secretion and obtained only 2 that were positive for the organism.

Other investigators have found unusually high rates of incidence. Nitschke demonstrated the presence of the parasite in 5 of 40 cases of so-called nonspecific urethritis. He believed that T. vaginalis was present in a fair percentage of the discharges of patients with so-called nonspecific urethritis.

Other authors examined the husbands of women with T. vaginalis infection and found that a relatively high number of them were likewise infected. Drummond found that 4 out of 5 such husbands examined were infected with T. vaginalis. Karnaky demonstrated that 38 of 150 men examined were infected with this organism.

ETIOLOGIC FACTORS AND PATHOGENESIS

The explanation of Trichomonas infection in men is unknown. Leaving aside the personal opinions of authors, we find two types of statistics. One set of figures tends to prove that sexual relations of men with infected women are the most probable source of the disease. For example, Drummond demonstrated T. vaginalis infection in 80 per cent of the husbands of infected women, and Karnaky, in 25 per cent.

On the other hand, it must be remembered that according to Stuhler the incidence of T. vaginalis infection in all adult women is 40 to 60 per cent, and in those with leukorrhea, 75 per cent. Despite this impressive rate of incidence in women, Stuhler found T. vaginalis infection in only 0.05 per cent, and Riba, in 0.06 per cent of the men examined.

A damaged or chronically inflamed urethra with lowered resistance seems to favor Trichomonas adaptation and local morbidity and to provide a source for dissemination of the parasites. Out of 23 patients whose records were in Riba and Harrison's office files, 65 per cent admitted previous gonococcic infection; for another 10 per cent there was no information, and 25 per cent gave a history of previous urethral stricture.

The sites of infection in men may be single or multiple. In a series of 23 cases T. vaginalis was found in the fresh urethral discharge in 11, in the prostatic secretion in 17 and in the fresh urinary sediment in 16. Karnaky took specimens from under the prepuce. Madsen found a case of T. vaginalis infection of the renal pelvis and stated that only 1 other case had been reported.

PATHOLOGY

No good descriptions of the gross lesions of the mucosa in men are available.

As early as 1929 Riba and Perry noted the occurrence of prostatovesiculitis. Heckel observed on rectal examination that the prostate may

be normal in size, shape and consistency or that there may be areas of hardness or infiltration.

Of Riba and Harrison's 23 patients, 61 per cent had urethral stricture; 25 per cent of these gave a history of previously discovered and treated urethral stricture. Of all the cases of urethral stricture of which they had record in their files, Trichomonas was identified in 10 per cent. It is evident that T. vaginalis was the cause of some of the strictures or tended to settle in urethras which had preexisting strictures.

SYMPTOMS AND SIGNS

Most reports show that men who have this disease present symptoms and signs. One sign observed by most authors is a discharge. It was present in 80 per cent of Riba and Harrison's series and was a mucoid or purulent urethral discharge. Melvin as well as Nitschke found that the patients complained of a watery discharge from the urethra. Heckel recorded that the disease sometimes started as acute urethritis in which the discharge had a frothy, bubbly appearance.

Heckel stated that the symptoms of Trichomonas infection of the prostate are the same as those of nonspecific urethritis, persistent urethral discharge and morning drop associated with various other genitourinary complaints. His description of the prostate from rectal examination has already been given. He stated that it is never tender or swollen as in acute gonorrheal prostatitis.

Manwell noted the relationship of urinary symptoms to Trichomonas infection, even though other authors have failed to observe this.

In some of Karnaky's cases there was itching of the glans penis.

LABORATORY DIAGNOSIS

The disease is not common. However, there are probably more cases than are diagnosed.

To find more of these cases and attempt to clarify a good many points about this disease in men, we suggest that appropriate specimens be taken as regularly as feasible in general examinations. Appropriate specimens should be obtained from all men with nonspecific urethritis. Husbands of women with T. vaginalis infections should be carefully investigated.

Methods of Collecting Specimens.—Specimens should be obtained from the prepuce, the urethra, the urine and the prostate. It must be remembered that the fragility of T. vaginalis precludes successful detection unless care is exercised in handling.

If there is sufficient material, the prostatic fluid is allowed to drip directly into an open sterile Petri dish, 7.5 cm. in diameter. The dish is then covered.

If there is only a scanty amount of fluid, separate sterile cotton-tipped applicator sticks are used to collect material from the prepuce, the urethra and the prostate.

The swab is small, not over 3 mm. in diameter. It is tightly wound so that the flagellates will have difficulty in penetrating between the cotton fibers. If they do penetrate and become enmeshed in the fibers below the surface, they are probably lost for purposes of identification because, through adherence, among other factors, they will be trapped, and the examiner will be unable to express them onto the slide.

Immediately after the specimen is taken, the cotton-tipped end of the swab is placed in a separate small sterile test tube containing 0.5 cc. of 0.85 per cent sodium chloride solution. Each tube has a sterile nonabsorbent cotton stopper, which is put back in place as soon as the applicator stick is inserted.

Urine is collected in a sterile container.

Dry smears are made of prostatic and urethral material in the usual manner. These are appropriately stained and examined, particularly for gonococcus, Streptococcus subacidus and Monilia albicans.

Methods of Examination.—It is our experience that accurate reports on Trichomonas can be made only by the advanced laboratory worker.

(*a*) Direct Examination of Specimens Obtained in Small Petri Dishes: A sufficient amount of the fluid is removed from the Petri dish with a sterile Pasteur pipet having a long tip of capillary diameter. The fluid (0.01 cc.) is placed on a sterile glass slide kept at a temperature approximating 90 F. It is covered with a sterile no. 1 cover slip. Microscopic search is instituted with a magnification of approximately 640 (10x oculars and high dry objective). If no movement is noted, additional preparations are examined, fifteen minutes each, before being pronounced negative. If kept at 98.6 F., trichomonads are viable in prostatic secretions for an average period of six hours.

(*b*) Examination Following Centrifugation of Wet Specimens: In our opinion this has not been a common enough practice. Tests should not be pronounced negative until this method has been employed.

For specimens obtained in sodium chloride solution, the procedure is as follows: If a prolific discharge has not been obtained, the swab is thoroughly rinsed in the solution, being pressed and rotated against the wall of the test tube to express as much liquid as possible, before it is discarded. The sterile conic test tube is centrifuged for five minutes at 3,000 revolutions per minute. The supernatant fluid is removed, and the sediment in the bottom of the tube is placed on a sterile glass slide under conditions similar to those described for direct examination. Trichomonads adhere to the fibers of the swab, and this makes it necessary to handle it as described. Omission of centrifuging would leave the parasites in far too dispersed a condition to be studied conveniently. The importance of these maneuvers is seen in the fact that Magath, who merely shook these swabs, obtained positive evidence of T. vaginalis infection in only 20.8 per cent of his series of 250 women.

In cases in which the discharge has been fairly prolific, the swab is pressed firmly against a slide and rotated with continuous maintenance of pressure at an angle of approximately 30 degrees from horizontal. Magath, who merely shook these swabs onto the slides, reported that 1.92 per cent of his cultures were failures.

Urinary specimens are centrifuged and mounted in the same way as specimens of nonprolific discharge in solution of sodium chloride.

(*c*) Methods of Examination Not Ordinarily Utilized: Certain maneuvers are of value to the research worker and advanced technician. For instance, determination may be made of the number of trichomonads present in a measured volume of solution.

Differential Characteristics of Species of Trichomonas

Species	Structure						Incidence in Temperate Zone, per Cent	Culture		
	Variation in Length, Microns	Average Length, Microns	No. of Anterior Flagella	Parabasal * Apparatus	Size of Chromatic Basal Rod and Axoneme	Cytoplasm	Usual Habitat		Optimal Mediums †	Gas Production	Odor
T. vaginalis....	7 to 23	13	4	Sausage-shaped	Less than one-half the body length	Granules seen; vacuoles rare; light-staining	Genitourinary tract	50 to 60 (women)	L. E. S. or placenta agar	Very marked with pressure	Foul and slightly pungent
Trichomonas hominis	7 to 14	8	3 to 4	Oval	Nine-tenths to entire body length	No granules seen; vacuolated; deep-staining	Intestine	1.7	L. E. A. or blood agar	Small	Unpleasant
Pentatrichomonas ardin deltelli	6 to 16	9	5								
T. buccalis.....	6 to 12	7.5	4	Biscuit-shaped	Three-fourths body length	Few granules with no definite arrangement; vacuolated; deep-staining	Mouth	18 to 24	L. E. S. or placenta agar	Moderate	Foul, like bad breath

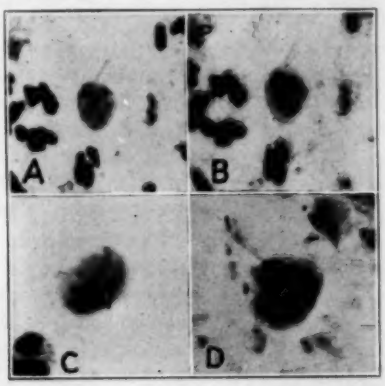
* Visualized only with stains containing osmic or chromic acid.

† L. E. S. indicates Boeck and Drbohlav's Locke solution-egg-serum medium, in which equal parts of Locke solution and human blood serum are added to egg slants prepared with Locke solution. L. E. A. indicates Drbohlav's modification of the aforementioned medium, in which a 1 per cent solution of crystallized egg albumin in Locke solution is substituted for the mixture of Locke solution and human blood serum. The formulas for these mediums are contained in Craig, C. F., and Faust, E. C.: Clinical Parasitology, ed. 2, Philadelphia, Lea & Febiger, 1940, p. 660.

There are also cultural methods which are most useful for making blood examinations, for increasing the total number of trichomonads prior to staining for species identification and for differentiation of the species. The traps of Stone and Reynolds give bacteria-free cultures of T. hominis and are apparently applicable in pure culture studies of the three common species of Trichomonas. The cultural characteristics of the different species are given in more detail in the table.

There are two methods which we do not recommend. Moist preparations stained with 0.1 per cent safranine are used mainly for the differentiation of T. vaginalis from pus cells, but since safranine is a negative stain, its accuracy is dubious. The hanging drop procedure is valuable but time consuming and, in our opinion, unnecessary. Trichomonads are not crushed by the pressure of a cover slip.

Identification of T. Vaginalis (photomicrograph).—Identification of T. vaginalis is made on the basis of the motility, the manner of progress, the gross appearance and the size of the flagellate. The parasite is motile. The anterior flagella have a peculiar whiplike motion, which in an active trichomonad occurs with a simul-



Photomicrographs of Trichomonas vaginalis; hematoxylin stain; × 1900.

A, usual body form of the young flagellate. *B*, an artificial light cone sometimes confused with the cyst form. Note the two visible flagella. *C*, surface focus, showing chromatic basal rod extending across cytoplasm and starting from anterior blepharoplast. *D*, form often seen in heavy infections; the two flagella are again visible. Note the granules in the cytoplasm.

taneous forward propulsion and counterclockwise rotation. If the flagellate is hindered by pus and epithelial cells or its motion is reduced, one may see that one flagellum whips forward and backward over the body surface, while the others appear to move forward only as far as the anterior plane and then back. This differential motion of the flagella helps to distinguish the trichomonads from other protozoa which may be present. The organism without the flagella is 8 to 16 microns in width and 15 to 26 microns in length.

It may be of vital interest to differentiate T. vaginalis from the other species of Trichomonas. The table may prove of assistance.

TREATMENT

The treatment of this infection in men has been multifarious and disputed and consequently somewhat confusing. In general, the forms of

therapy have been those generally used by the specialist in genitourinary diseases of men.

Much more definite advances have been made in the treatment of T. vaginalis infections in women because of the larger number of cases. Two compounds, acetarsone and silver picrate, have been used with considerable success. The literature is replete with articles attesting their therapeutic efficacy. In treating a man, it seems logical to use one of the aforementioned antiseptics which have already proved their parasiticidal action on T. vaginalis in numerous cases of infection in women.

An acetarsone preparation is incorporated into a 2 inch (5 cm.) size 14 (French) urethral suppository. The patient is instructed to insert this after allowing warm water to run on it for a short time so that it will mold more easily to the contour of the urethra. One is inserted after urination in the morning and evening. To obtain prostatic smears, the prostate is massaged lightly about every third day for ten days and every two weeks for about two months.

Although it has not been proved that a woman can reinfect a man, it seems best to have the patient use some precautions. It is not wise for him to have sexual intercourse during the period that specimens obtained from him show T. vaginalis. For a few weeks after such a period it is probably best that he use condom protection. It would be interesting to cure the man but not the woman and then observe the effects of intercourse on the man. However, from a nonexperimental standpoint it is more acceptable to treat the disease in the woman coincidentally with that in the man.

The rapid cure of urinary symptoms in the case to be reported gave rise to an idea which it is proposed to use in the treatment of women with T. vaginalis infection and urinary symptoms. The clearing up of urinary symptoms is often delayed in these patients, even though the Trichomonas infection of the vagina is receiving adequate therapy. Of course, proper treatment will be administered for the Trichomonas infection of the vagina, but in addition urethral suppositories incorporating an acetarsone preparation will be used twice daily in these women to see whether a quick cure of the annoying urinary symptoms cannot be obtained.

REPORT OF A CASE

G. M., a 25 year old white man, a university student, was first seen Sept. 5, 1940. He had had sexual intercourse with one woman on repeated occasions in the preceding three months. Two weeks prior to his first reporting to us, he had had intercourse without protection on the last night of the woman's menstrual period.

Five days later he had a burning, irritated feeling just inside the external urethral meatus. After six more days he had a feeling of general debilitation, a dull ache in his penis and an increased tendency to urinate accompanied by tenesmus and burning. He denied that he had used therapy of any kind, that there

had been any discharge from the penis or that there had been previous venereal or genitourinary infections.

Physical examination revealed no urethral discharge. The prostate showed 2 plus enlargement (on a basis of 1 to 4) and irregular areas of 2 plus hard infiltration. The urethra and prepuce were normal. A direct prostatic specimen showed four to five trichomonads identified as T. vaginalis per high dry field. The dry smear had no intracellular or extracellular gram-negative diplococci, Streptococcus subacidus, Monilia albicans or pus cells.

Twelve urethral suppositories incorporating an acetarsone preparation were prescribed; this was the total extent of the medication. He was told to use one before retiring and in the morning after urination. The prostate was massaged on September 7 and 10, there being only one-third as much enlargement and one-half as much hard infiltration on September 10 as on September 5. Specimens of prostatic fluid taken on September 13, 16 and 22 and October 8 and 18 were uniformly negative for T. vaginalis. The patient was free of symptoms by September 10.

The woman was found to have T. vaginalis infection and quickly responded to therapy.

The patient had protected intercourse with the same woman on September 16. He continued in this manner about twice a week until October 17, after which he had unprotected intercourse without reinfection of himself or the woman.

COMMENT

While certain of the laboratory methods which we have described may have been utilized by other workers, search of the literature to date fails to reveal publication of the following facts:

1. It is advantageous to allow the prostatic fluid to drip directly into the Petri dish; this minimizes manipulation and contamination.

2. The relatively sterile technic used to eliminate contaminating organisms makes it possible to report the identification of protozoa, bacteria and fungi with more assurance than with any previously used easy technic that we have been able to find.

3. The improved type of swab which we have described helps to minimize the percentage of falsely negative reports.

4. The careful expression of the liquid material from the swabs, a hitherto unpublished method, has advantages, which we have carefully enumerated.

5. The routine centrifuging of wet specimens which is strongly urged, coupled with the careful, time-consuming laboratory examination, gives the worker a more reasonable sense of satisfaction when he reports a specimen as negative for Trichomonas.

6. The careful use of the description of T. vaginalis and the easily available information in the differential diagnostic table (which, by the way, is the first of its kind published) certainly minimizes the percentage of errors. However, if a person is unable to recognize the organism for which he is looking, all the refinements mentioned would obviously be

futile. No claims are made that every one can identify this flagellate. In the table special attention must be paid to the chromatic basal rod and axoneme, under "Structure." The axoneme, of course, includes the attached portion of the posterior flagellum. Therefore, the point of emergence of the posterior flagellum is of great diagnostic importance.

A new method of treatment for Trichomonas infection in men has been presented. Attention has been called to the fact that this mode of therapy may be of value in curing the urinary symptoms sometimes encountered in T. vaginalis infections of women. Since 40 to 60 per cent of women have this infection, it appears that this proposed therapeutic method is worth cognizance and experimental trial.

SUMMARY

The diagnosis, particularly from a laboratory aspect, of Trichomonas vaginalis infections of the male genitourinary tract is presented in some detail.

A new form of treatment for Trichomonas infection in men is given. This method may prove of value in certain aspects of the disease sometimes encountered in women.

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MEDIASTINAL EMPHYSEMA AND BILATERAL PNEUMOTHORAX FOLLOWING RADICAL DISSECTION OF THE NECK

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Surgical procedures about the neck which allow ample opportunity for partial blocking of the upper respiratory passages and for opening the mediastinum provide a situation most favorable for the development of mediastinal emphysema. Berry [1] reported 4 cases of thyroidectomy and 1 of tracheotomy in which mediastinal emphysema and bilateral pneumothorax were present at death, which occurred either on the operating table or shortly afterward. At autopsy, in every case, the pleura was intact, and there was no interstitial emphysema present; air, then, must have entered through the operative site. Keis [2] reported 8 cases of thyroidectomy, in 5 of which mediastinal emphysema was observed at autopsy. In 4, bilateral pneumothorax was present. In all of these cases, the tracheal and bronchial passageways were normal, and the lungs showed no interstitial emphysema.

Keis expressed the opinion that mediastinal emphysema occurring during operations on the upper portion of the neck is less frequent in young people because the thymus and healthy mediastinal connective tissue protect the patient from the development of this complication. In the older group, previous infection in or around the mediastinum with the formation of adhesions may serve to block the entrance of air at the time of operation.

REPORT OF A CASE

G. C., a 58 year old man, was first admitted to the Ellis Fischel State Cancer Hospital on Sept. 11, 1940. In 1936 a cancer of the lip had been treated elsewhere with a white powder. In August 1940, the lip became somewhat swollen, slight ulceration occurred at the site of the previous lesion of the lip, and small lumps were noted in the neck. The past history was noncontributory.

From the Ellis Fischel State Cancer Hospital, Columbia, Mo.

1. Berry, H. J.: Interstitial Emphysema and Pneumothorax After Operations, Lancet **1**:996, 1940.

2. Keis, J.: Studien zur Genese des Mediastinalemphysems und des Pneumothorax bei Kropfoperationen, München. med. Wchnschr. **81**: 669, 1934.

Physical Examination.—The patient was a well developed and well nourished man. The teeth were extremely carious. An ulcerating, fungating mass measuring 5 by 5 by 2 cm. replaced most of the lower lip and extended down to the chin. The lesion involved the right oral commissure. Enlarged lymph nodes were palpable in the submental and right submaxillary triangles and in the deep cervical region. The largest node was located in the submaxillary triangle and measured approximately 2 cm. in diameter. The lungs were clear and the heart normal. The blood pressure was 120 systolic and 85 diastolic.

Laboratory Examination.—The urine showed a slight trace of albumin. The blood was normal. Three biopsies of the lesion of the lip showed hyperkeratosis and chronic inflammation.

Clinical Course.—The patient was given an intensive course of roentgen therapy to the lip and to the lymph nodes of the upper cervical region. This treatment resulted in marked regression of the lesion and some decrease in the size of the metastatic nodes. He was discharged from the hospital on November 10.

Second Admission.—The patient was readmitted on December 6. The lip showed a rather large defect, the edges of which were entirely healed, soft and pliable. There was no clinical evidence of residual carcinoma in the area of the primary lesion. The previously described mass in the submaxillary triangle had increased to 2.5 cm. in diameter but was not attached to the mandible. Posterior to this and beneath the tail of the parotid gland was another mass which measured 1 cm. in diameter. In the submental triangle and the deep cervical chain, involvement of the lymph nodes was not apparent. Complete dissection of the right side of the neck and the submental triangle was thought advisable.

Surgical Procedure.—On December 12, with the patient under anesthesia induced by administration of avertin with amylene hydrate followed by insufflation of ether, a complete dissection of the right side of the neck was started. After elevation of the flaps, the sternocleidomastoid muscle was sectioned from its inferior attachment, and the internal jugular vein was isolated, doubly ligated and sectioned just above its junction with the subclavian veins. Suddenly, while the work in this area was going forward, a sucking and blowing noise was heard. It was thought that the apical parietal pleura had been opened, and the area of questionable defect was carefully closed with interrupted silk sutures, after which the sound stopped.

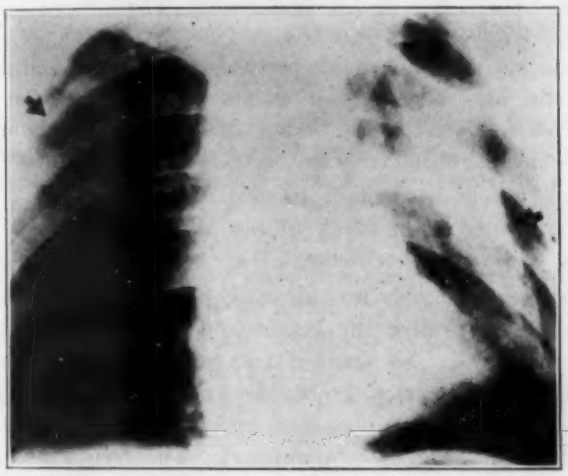
As the operation progressed, an occasional slight sucking noise was heard, but repeated investigation failed to reveal its cause. The operation otherwise proceeded uneventfully, except for some difficulty in maintaining a perfectly free airway.

Throughout this three hour procedure, the blood pressure and pulse remained at a constant normal level. The patient showed no signs of anoxemia or cyanosis until the operation was nearly terminated, when sudden and extreme cyanosis developed. Oxygen was administered through a tracheal catheter, and artificial respiration was given. In spite of these measures the patient's condition grew steadily worse, and he died in cardiorespiratory failure.

After death, a needle was inserted into the right pleural cavity, and 20 cc. of air was removed. A postmortem anteroposterior roentgenogram of the chest was taken, and evidence of mediastinal emphysema and bilateral pneumothorax was seen. Unfortunately, no lateral views of the chest or roentgenograms of the abdominal cavity were taken.

Autopsy.—The anatomic diagnoses were: subcutaneous emphysema, mediastinal emphysema, bilateral pneumothorax, distention of the stomach, hemangiomas of the liver, adenomas of the kidneys, polyposis of the large bowel, benign hypertrophy of the prostate gland and cortical adenoma of an adrenal gland. The microscopic diagnoses confirmed the gross. Section of the surgical specimen showed epidermoid carcinoma present in a large node of the submaxillary triangle. All other nodes were free of evidence of tumor.

The body was fairly well developed. There was pronounced postmortem lividity of the face and dependent portions. There was slight subcutaneous emphysema in the loose tissues of the neck just above the sternum. When the peritoneal cavity was opened, the right diaphragm was strikingly convex. Bilateral pneumothorax was demonstrated by the puncture of both rib cages under water. With the removal of the sternum, numerous blebs were seen in the soft fatty



Bilateral pneumothorax. The arrows indicate the edges of the partially collapsed lungs.

tissue overlying the heart. Emphysema extended throughout the anterior and posterior mediastinum.

The lungs showed no evidence of interstitial emphysema. There were old bilateral adhesions, causing complete obliteration in the upper thirds of both pleural cavities. Rupture of mediastinal blebs with separation of the parietal and visceral pleura had caused formation of bilateral pneumothorax. This bilateral pneumothorax was not complete because tough fibrous adhesions between the parietal and visceral pleura at the apexes prevented total collapse of the lungs.

Careful attention was given to the parietal pleura in the right apex, but no evidence of a surgical wound was found.

The heart weighed 300 Gm.; slight dilatation of the right auricle was evident. The stomach was much distended, and on puncture a large amount of air smelling of ether rushed forth. There were small hemangiomas in the liver. Tubular adenomas in the kidneys measured from 5 mm. to 1 cm. in diameter. A marked polyposis of the ascending colon was present.

COMMENT

Macklin,[3] experimenting with cats and other animals, demonstrated the pathway by which air can reach the mediastinum from the upper respiratory passages. Under increased pressure air breaks through alveoli, reaches the interstitial tissues, travels along the sheaths of the pulmonary veins and arteries, and finally enters the mediastinum. If air continues to be pumped into the mediastinum, the rupture of emphysematous blebs on the mediastinal pleural surface may cause unilateral or bilateral pneumothorax. Therefore, if this mechanism had been at work in our case, there should have been some interstitial emphysema; careful examination at autopsy showed none. Direct entrance of air through the wall of any thoracic organ into the mediastinum may cause mediastinal emphysema. There was no evidence of any break in the continuity of the mucosa of the bronchi, trachea or esophagus.

Infections such as influenza,[4] pertussis, diphtheria and other acute diseases of the lung may provide an entry for air into the interstitial tissue. Gross and microscopic examination of the lungs in our case showed no evidence of infection in the trachea, bronchi or alveoli.

Hamman [5] wrote of spontaneous mediastinal emphysema, but that is always accompanied by a break in the alveolar wall with interstitial emphysema, and, as has been stated, there was none of this in our case.

We believe that the only way air could have entered the mediastinum was through the operative site because no interstitial emphysema was present in the lungs. Air could not have entered the pleural cavities through the surgical incision directly, because the pleura of the left lung was not approached by the dissection and because autopsy revealed the pleura of the right lung to be uninjured. The pleural spaces in both apexes were obliterated by adhesions. The presence during the operation of some obstruction to the airway increased the intrathoracic negative pressure on inspiration and induced air to enter the thorax through the only other opening available. With each inspiration air was sucked into the open anterior mediastinum, where it became trapped in the soft tissues. As the condition progressed, large blebs of air appeared beneath the mediastinal pleurae, and it was the rupture of these that produced pneumothorax.

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3. Macklin, C. C.: Transport of Air Along Sheaths of Pulmonary Blood Vessels from Alveoli to Mediastinum, Arch. Int. Med. **64**:913 (Nov.) 1939.

4. Torrey, R. G., and Grosh, L. C.: Acute Pulmonary Emphysema Observed During the Epidemic of Influenzal Pneumonia at Camp Hancock, Georgia, Am. J. M. Sc. **157**:170, 1919.

5. Hamman, L.: Spontaneous Mediastinal Emphysema, Bull. Johns Hopkins Hosp. **64**:1, 1939.

It is conceivable that with the development of mediastinal emphysema there will be increasing obstruction to venous return. The mechanical and physiologic changes are similar to those found in cardiac tamponade. In the case presented, bilateral pneumothorax added further embarrassment to the respiratory mechanism, and with the pulmonary collapse oxygen exchange was interfered with to such an extent that the patient died of heart and respiratory failure.

Artificial respiration was probably contraindicated, for, as Keis [2] mentioned, this tends to increase mediastinal pressure and facilitate the production of pneumothorax.

The presence of multiple hemangiomas of the liver, tubular adenomas of the kidneys, cortical adenoma of an adrenal gland and marked polyposis of the large bowel causes speculation as to whether or not some congenital anomaly might not have existed in the mediastinum.

PREVENTION AND TREATMENT

During an operation in the lower portion of the neck the possibility of the development of mediastinal emphysema should be kept in mind. Prevention can best be accomplished by making certain that a perfectly free airway is maintained when the limits of the mediastinum are approached.

It is extremely important to recognize the condition in its early stages, since the establishment of an adequate airway will decrease the negative intrathoracic pressure on inspiration and may help prevent abnormal ingress of air into the thorax. If the establishment of an adequate airway does not suffice, the opening into the mediastinum should be closed by packing or closing the soft tissues or by terminating the operation and closing the wound if necessary. In our case the surgeon did not appreciate the situation and was misled to believe the sucking noises were the result of a small leak through the parietal pleura. The signs were insidiously unimpressive until the sudden and complete collapse of the patient.

If mediastinal emphysema is not recognized until after bilateral pneumothorax has occurred, emergency aspiration of both pleural spaces should be done. If aspiration by syringe and needle does not afford adequate decompression, an intercostal catheter may be inserted into the chest and connected to a suction apparatus or to a water-sealed drainage bottle. Artificial respiration is contraindicated.

Mediastinal emphysema is probably much more frequent than is suspected. Failure to think of this complication during an operation on the neck, failure to take roentgen films of the chest and, if the patient dies, failure to check for pneumothorax and to look for mediastinal emphysema may result in an erroneous diagnosis.

A provisional diagnosis can be verified by roentgen examination of the chest; lateral films are particularly valuable in demonstrating the mediastinal air. If the emphysema is extreme, pneumoperitoneum may be demonstrated by a roentgenogram of the abdominal cavity.

SUMMARY

A case of mediastinal emphysema with bilateral pneumothorax, with death following radical dissection of the neck is reported. The cause, mechanism, treatment and prevention of the condition are discussed.

STORED DEXTROSE-CITRATE PLASMA IN THE TREATMENT OF OPERATIVE SHOCK

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There have been several reports dealing with the value of plasma in the treatment of shock.[1] This has been the result of the establishment and general acceptance of certain tenets concerning plasma: (1) transfusions of plasma may be given without regard to blood groups; (2) plasma may be obtained from stored whole blood that is too old to use as it is; (3) plasma may be stored for long periods and remain efficacious. The purpose of this paper is to report certain experiences acquired by using plasma in the treatment of shock associated with operative procedures in the surgical service of the University Hospitals.

TYPE OF SHOCK ASSOCIATED WITH OPERATIONS

The problem of defining clinical shock offers considerable difficulty. Certain authors have separated shock and hemorrhage and have described distinguishing features for each. It remains, however, the general practice to designate as shock conditions in which there is an acute lowering of blood pressure. I have found it practical to consider "shock associated with operations" as a broad term describing a state of circulatory

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This study was made in cooperation with Dr. Elmer J. DeGowin, Department of Medicine.

1. (*a*) Elliott, J.; Busby, G. F., and Tatum, W. L.: Preparation and Preservation of Dilute Plasma, J. A. M. A. **115**:1006 (Sept. 21) 1940. (*b*) Strumia, M. M.; Wagner, J. A., and Monaghan, J. F.: Use of Citrated Plasma in Treatment of Secondary Shock, ibid. **114**:1337 (April 6) 1940. (*c*) Levinson, S. O.; Neuwelt, F., and Necheles, H.: Human Serum as a Blood Substitute in the Treatment of Hemorrhage and Shock, ibid. **114**:455 (Feb. 10) 1940. (*d*) Tatum, W. L.; Elliott, J., and Nesset, N. M.: A Technic for the Preparation of a Substitute for Whole Blood Adaptable for Use During War Conditions, Mil. Surgeon **85**:481 (Dec.) 1939. (*e*) Lehman, E. P.: A Simple Method of Plasma Transfusion, Correspondence, J. A. M. A. **112**:1406 (April 8) 1939. (*f*) Mahony, E. B.: Study of Experimental and Clinical Shock with Special Reference to Its Treatment by Intravenous Injections of Preserved Plasma, Ann. Surg. **108**:178 (Aug.) 1938. (*g*) Bond, D. D., and Wright, D. G.: The Treatment of Hemorrhage and Traumatic Shock by the Intravenous Use of Lyophile Serum, ibid. **107**: 500 (April) 1938.

insufficiency in which there is a fall of the systolic blood pressure below 80 mm. of mercury. The circulation does not function efficiently when the arterial tension is lower than this value. One may then recognize several types of shock. Primary or neurogenic shock is essentially a vasomotor phenomenon, characterized by arteriolar relaxation without hemoconcentration; usually in this type the pulse rate is not increased. Spinal anesthesia frequently causes this syndrome, which, if not relieved, may develop into secondary shock. Secondary shock, often called surgical or traumatic shock, is characterized by capillary dilatation, atonicity and increasing permeability; this type results in hemoconcentration. According to Moon,[2] this is the only condition that should be considered as true shock. Shock secondary to hemorrhage is brought about by the decrease in circulating blood volume caused by loss of both plasma and red cells. At first there is a tendency toward hemoconcentration of the remaining blood; later, hemodilution occurs.

One feature of shock, regardless of type or causative factors, is reduced circulating blood volume. In severe shock crystalloid solutions injected intravenously pass quickly out of the vascular system into the tissues and produce only a transient increase in circulating blood volume. Plasma, serum and lyophil serum, however, are retained in the vascular system and contribute a more permanent increase in circulating blood volume.[1e, f, g]

GENERAL CONSIDERATIONS CONCERNING THE USE OF DEXTROSE-CITRATE PLASMA

In the blood bank of the University Hospitals, blood is stored in the Rous-Turner dextrose-citrate mixture, as modified by DeGowin, Harris and Plass.[3] This mixture consists of 10 volumes of blood, 13 volumes of 5.4 per cent dextrose in water and 2 volumes of 3.2 per cent sodium citrate (dihydric) in water. Blood is stored in this mixture at 2 C. for thirty days before it is considered unfit for transfusions. At the expiration of the limit of storage, the supernatant dextrose-citrate plasma is pipetted off from the sedimented erythrocytes and the latter discarded. Thereafter the dilute plasma is kept refrigerated and employed in the treatment of operative shock. No antiseptics are added to the plasma mixture. The concentration of free hemoglobin in the dilute plasma is always less than 25 mg. per hundred cubic centimeters. Transfusions of the plasma mixture are given without

2. Moon, V.: Shock and Related Capillary Phenomena, New York, Oxford University Press, 1938.

3. DeGowin, E. L.; Harris, J. E., and Plass, E. D.: Studies on Preserved Human Blood: I. Various Factors Influencing Hemolysis, J. A. M. A. **114**:850 (March 9) 1940.

regard to the isoagglutinins. Eighty-nine plasma transfusions have been given, of which twenty-six were employed in the treatment of shock. No transfusion of the latter series was accompanied by chills or fever. The only febrile reaction encountered in the entire series occurred in a patient receiving his sixth plasma transfusion for the supplement of plasma proteins.

Since hemorrhage, neurogenic reflexes and tissue trauma all play a part in causing the shock that is seen in patients during or following operations, it is sometimes difficult to assign the condition to any one of the aforementioned three categories. With current anesthetic methods and preoperative preparation, severe shock associated with general surgical operations is infrequent. During the year 1939 there were 1,892 major operations performed by the general surgical staff at the University Hospitals. There were 68 instances of secondary shock or shock secondary to hemorrhage during or after the operations. There were 50 cases of primary shock, in all of which this condition was alleviated without intravenous injection of fluid. In several cases in this series the condition could be classified as mild shock.

EFFICACY OF PLASMA IN THE TREATMENT OF SHOCK

Dextrose-citrate plasma was given to 26 patients who manifested shock during or after operations. Data on 18 of these patients are given in the table. Hematocrit determinations were made before operation, at the beginning of plasma transfusion, on the day following operation and on subsequent days. In every case a satisfactory recovery from a state of shock ensued. The amount of blood lost during operation was determined by dissolving the hemoglobin from the sponges and drapes in water, and determinations of hemoglobin were made by using the Kletts-Summerson photocolorimeter. The patient's hemoglobin had been determined before operation, and by proportion to the amount of hemoglobin lost, the volume of blood lost was computed.

There is one question concerning the use of plasma which immediately presents itself: Is plasma alone adequate in the treatment of shock associated with severe hemorrhage? In most of the cases the loss of blood was moderate, but in 2 it was excessive. In case 1, the blood loss was 320 cc., which represented 23 per cent of the patient's estimated total blood volume. The hematocrit determination was 32 at the time plasma transfusion was started, and the child was then in severe shock. Shock was alleviated within thirty minutes, but eighteen hours later the hematocrit determination was 23, indicating marked anemia. One may state that dextrose-citrate plasma was highly satisfactory in alleviating shock in these cases, even when the

Patient, Sex and Age (Yr.)	Type and Time of Operation	Blood Loss (Per Cent of Total Volume and Cc.)	Clinical Condition When Treatment Was Begun	Quantity of Dextrose-Citrate Plasma Given (Cc.)	Result	Hematocrit Determinations									
						Before Operation	During Shock	Days After Operation							
								2	3	4	5	6	7	8	9	10
1 F 7	Sequestrectomy (45 min.)	23% (310 cc.)	B.P. 0/0; pulse weak; pulse rate 160; extremities cold	650	Response in 10 min.; recovery complete within 25 min.	..	32	23	22†	30	31	..	..	..	..	..
2 F 45	Repair of ventral hernia (3 hr.)	16% (960 cc.)	B.P. 78/60; pulse weak; pulse rate 128; perspiring; extremities warm	650	Recovery complete within 20 min.	45	45	33	31	..	..	..	31	..	..	34
3 M 43	Thoracoplasty, first stage (2½ hr.)	16% (920 cc.)	B.P. 60/40; pulse weak; pulse rate 120; perspiring	1,400	Recovery complete within 20 min.	52	44	38	36	..	37	..	..	..	..	..
4 F 44	Radical mastectomy (2¼ hr.)	14.5% (700 cc.)	B.P. 60/40; pulse weak; pulse rate 90; perspiring; extremities cold	650	Recovery complete within 30 min.	49	48	32	..	34	..	34	..	35	..	..
5 M 56	Abdominoperineal resection of the rectum (2 hr.)	10% (612 cc.)	(During operation) B.P. 20/0; pulse imperceptible; extremities cold and clammy	1,800	Response in 15 min.; B.P. 90/60 at end of operation; 30 minutes later, 120/80	41	39	32	..	28	..	33†	..	36	..	..
6 F 43	Radical mastectomy (2 hr.)	9.5% (412 cc.)	B.P. 50/0; pulse weak; pulse rate 110; perspiring; extremities warm	650	Recovery complete within 30 min.	42	38	30	..	29	..	29	..	30	..	..
7 M 30	Thoracoplasty, second stage (1½ hr.)	9.5% (500 cc.)	B.P. 70/50; pulse weak; pulse rate 120; perspiring; extremities warm	650	Recovery complete within 30 min.	47	46	38	..	35	..	36	..	..	..	..
8 M 34	Thoracoplasty, first stage (2 hr.)	9% (470 cc.)	B.P. 60/0; pulse weak; pulse rate 130; perspiring; extremities cool	700*	Recovery complete within 20 min.; given later transfusion	52	48	39	..	..	41	..				

8 M 34	Thoracoplasty, first stage (2 hr.)	9% (470 cc.)	B.P. 60/0; pulse weak; pulse rate 130; perspiring; extremities cool	700*	Recovery complete within 20 min.; given later transfusion	52	48	39	..	..	41	..			
9 F 36	Thoracoplasty, second stage (1½ hr.)	9% (420 cc.)	B.P. 80/60; pulse weak; pulse rate 140; perspiring; extremities cool	700*	Recovery complete within 30 min.	44	42	34	..	33	..	31	..	..	..	..
10 F 38	Radical mastectomy (3 hr.)	8% (500 cc.)	B.P. 80/60; pulse weak; pulse rate 130; perspiring; extremities warm	1,100	Recovery complete within 20 min.	40	38	30	..	28	..	30	..	32	..	..
11 F 41	Revision thoracoplasty (2 hr.)	7.5% (332 cc.)	B.P. 78/58; pulse weak; pulse rate 124; perspiring; extremities warm	650*	Recovery complete within 20 min.	40	39	26	..	27	..	28	..	..	..	..
12 M 29	Thoracoplasty, second stage (2 hr.)	7.5% (470 cc.)	B.P. 60/0; pulse weak; pulse rate 160; perspiring; cold, clammy, cyanotic	600	Recovery complete within 20 min.	46	46	37	..	36	..	36	..	..	..	..
13 F 40	Vaginal hysterectomy (1½ hr.)	Large	B.P. 70/40; pulse weak; pulse rate 140; perspiring; cold and clammy	625	Recovery complete within 30 min.	..	40	25	..	24	..	28	..	..	28	..
14 F 42	Nephrectomy (2 hr.)	Large	B.P. 72/38; pulse weak; pulse rate 130; perspiring; extremities warm	650	Recovery complete within 30 min.	..	34	29	..	21	..	22	..	..	..	..
15 M 71	Abdominoperineal resection of rectum (2 hr.)	7% (300 cc.)	B.P. 60/40; pulse weak; pulse rate 100; perspiring; extremities cold	1,200	Recovery complete within 20 min.	51	55	35	..	34	..	36	..	38	..	..
16 M 28	Exploratory laparotomy and appendectomy (1 hr.)	Small	B.P. 80/60; pulse weak; pulse rate 70; extremities warm (primary shock)	650	Recovery complete within 15 min.	..	48	47	..	..	..	..	..	..	..	..
17 F 40	Gastroenterostomy (1½ hr.)	Small	B.P. 80/60; pulse weak; pulse rate 80; warm (largely primary shock)	650	Recovery complete within 15 min.	37	36	38	..	42	..	42	..	..	..	..
18 F 58	Resection of ileum; anastomosis (case of intestinal obstruction) (3½ hr.)	Small	B.P. 70/60; pulse weak; pulse rate 120; perspiring; extremities warm	1,200	Recovery slow; B.P. 120/80 after 1 hr.; died on 3d postoperative day of peritonitis	52	55	44	..							

* These patients received dextrose-citrate plasma from Baxter flasks. Merthiolate was added as an antiseptic, and the flasks were stored at room temperature for periods of twelve, fourteen and sixteen weeks.

† Indicates transfusion of whole blood.

loss of blood had been relatively large. Considerable experimental evidence has been accumulated to show that a large percentage of red cells may be lost and yet adequate compensation will follow, provided that plasma is restored and oligemia thus prevented.[1c] Since both whole blood and plasma were available, it was thought inadvisable to use plasma and withhold whole blood in cases of severe hemorrhage merely to learn just how much loss of red cells the human organism is capable of withstanding, provided the volume is made up by plasma. Thus in craniotomies, in which the blood loss is often over 1,000 cc., preserved dextrose-citrate whole blood is used routinely.

There are some instances in which the use of plasma is preferable to that of whole blood. This is illustrated in the case of patient 18. She had an intestinal obstruction of four days' duration. At operation the obstruction was found to be due to adhesions, and resection of a loop of the ileum was necessary. The patient was markedly dehydrated on admission, and in spite of intravenous injection of fluids, the hematocrit determination was 52 when the operation was begun. Signs of shock were manifest after an hour, and at this time the hematocrit determination was 55. Thus there was considerable hemoconcentration, the viscosity of the blood was increased, and plasma was preferable to whole blood transfusion. Operations on the gastrointestinal tract usually cause hemoconcentration if they are not associated with considerable blood losses. When these patients have a high hematocrit determination before operation, the use of plasma is preferable to that of whole blood if shock is manifest. In any instance in which it is desirable to increase the circulating blood volume and red cells are not urgently needed, it may be argued that transfusions of plasma are preferable to those of whole blood since they do not carry the danger of hemolytic reactions.

Kekwick and co-workers [4] recently reported their experiences in the treatment of shock associated with air raid casualties. Multiple contusions, lacerations and compound fractures were frequent. The patients were usually seen one to three hours after injury and were in severe shock. Plasma was found effective in raising blood pressure, but it was often necessary to give 2,000 to 3,000 cc. to alleviate shock. The losses of circulating blood were often estimated to exceed 2,000 cc. In general, the hemoglobin determinations and hematocrit readings were normal on admission, but after recovery from shock, values were usually at least 50 per cent below normal. Thus there was a significant decrease in circulating red cells, and these workers formed the opinion that "when the amount of transfused fluid needed reaches three 540 cc.

4. Kekwick, A.; Maycock, W. d'A.; Marriott, H. L., and Whitby, L. E. H.: Diagnosis and Treatment of Secondary Shock, Lancet **1**:99 (Jan. 25) 1941.

bottles or more, at least one bottle in three should be blood." It is my opinion that plasma is efficacious in relieving operative shock when treatment is instituted immediately, even though there is associated a relatively large loss of blood. It should be noted, however, that the types of shock in my cases and in those of other American authors [1b] certainly are not comparable to the severe type of shock of several hours' duration that Kekwick and his associates have been called on to treat, and their conclusions regarding the desirability of whole blood appear logical.

SUMMARY

Stored dextrose-citrate plasma was efficacious in treating a series of patients manifesting shock associated with general surgical operations.

Plasma for this purpose may be obtained by aspiration of the supernatant fluid from blood stored for thirty days in dextrose-citrate preservative.

It is pointed out that treatment of shock in our cases was started immediately on development, and therefore our cases are not comparable to the cases of severe shock seen as a consequence of war injuries.

FOREIGN BODIES IN THE BILIARY TRACT

REPORT OF A CASE WITH A TABULAR REVIEW OF THE LITERATURE

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Foreign bodies in the biliary tract are of sufficient rarity to make the report of this case—in which a rubber catheter was present in the common duct—of interest. The fact that the lumen of a rubber tube may be obliterated by the deposition of bile salts is a serious objection to the use of rubber tubing in operations for the reconstruction of the biliary passages.

REPORT OF CASE

The patient, a 37 year old white woman, was admitted to the West Baltimore General Hospital April 10, 1935. She showed symptoms and signs suggestive of appendicitis, and a McBurney appendectomy was done. The gallbladder was said to be normal to palpation. The patient's postoperative course was uneventful, and she was discharged nine days after admission.

The patient was readmitted four months later with typical signs and symptoms of acute cholecystitis. At operation a gallbladder containing two stones was removed, and the hepatic and common ducts were observed to contain many stones. The common duct was opened, and the stones were evacuated. A Dakin tube was inserted through the stump of the cystic duct, and a size 20 F catheter was inserted into the common duct. Both of these tubes were sutured to the respective ducts with plain size 0 gut. The temperature was moderately elevated for several days following the operation. On the fourth day after operation an attempt was made to remove the catheter, but the distal 1½ inches (3.8 cm.) of the tube was accidentally broken off and left in the abdomen. The Dakin tube, however, was successfully removed. The further postoperative course was uneventful, and on the thirteenth day after operation a roentgenogram of the abdomen showed the distal portion of the tube to be in the right upper quadrant. On the eighteenth day the patient was discharged.

The patient had no further difficulty until about four years later, when she began to have attacks of pain in the right upper quadrant radiating to the subscapular region and nausea, vomiting, belching and, occasionally, jaundice. These attacks were infrequent at first but later became closer together and more severe.

On physical examination the patient was noted to be an apprehensive, well developed and well nourished woman of some 40 years, who was lying in bed with no apparent pain. The temperature and the pulse rate were within normal

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From the surgical service of Dr. E. S. Johnson at the West Baltimore General Hospital.

Author and Date	Age of Patient	Symptom-Free Interval	Symptoms	Nature of Foreign Body	Site of Foreign Body	Manner of Reaching Bile Duct	Length of Time in Bile Duct	Calcareous Deposits	Result
Oppel: Zentralbl. f. Chir. **53**: 889, 1926	?	?	?	Swab	Common duct	Probably migrated from peritoneum	4 mo.	?	Death from peritonitis
Lemierre and Pollet: Bull. et mém. Soc. méd. d. hôp. de Paris **51**: 241, 1927	40	?	"Stitch" in lower part of thorax; dry cough without expectoration; emaciation	Handle of spoon 13.5 cm. long	Handle was in common duct and extended to liver	Ingested by insane patient	?	Spoon handle markedly oxidized	Death
Fedoroff: Zentralbl. f. Chir. **57**: 657, 1930	39	2½ yr.	Attacks of colic; occasional jaundice	Horizontal part of T tube 6 cm. long	Retroduodenal part of common duct	Broke off at operation on attempted removal	4½ yr.	Covered with "Gallensand"	Recovery
Goldhan: Zentralbl. f. Chir. **57**: 2664, 1930	36	14 yr.	Severe pain	Copper bullet	Cystic duct	Bullet wound	15 yr.	The bullet was covered with a gritty brownish precipitate	Recovery
Elcheiter: Zentralbl. f. Chir. **58**: 674, 1931	39	15 mo.	Pain in right upper quadrant of abdomen with jaundice	Cotton fibers	Common duct	From drain at operation	17 mo.	The cotton fibers were encrusted	Recovery
Cook: Brit. M. J. **1**: 840, 1932	65	?	Indigestion; emesis; pain in right upper quadrant of abdomen	Piece of L-shaped wire less than 1 inch (2.5 cm.) long and 0.001 inch (0.0025 cm.) thick	Common duct	Probably ingested	?	None	Recovery
Toland: Ann. Surg. **98**: 604, 1933	49	Approximately 4 mo.	Jaundice and anemia	Cotton gauze 1 by 1 by 5 cm.	Common duct	Operation	6 mo.	The gauze was impregnated with bile salts and fibrin	Death
Crawford and Stewart: Am. J. Clin. Path. **9**: 363, 1939	33	3 wk.	Painless jaundice with clay-colored stools and hemorrhage	Hemostat blade 4.2 cm. long	Hepatic duct	Operation	7 yr.	The blade was covered with dark green friable pigment concretion	Death
Bowen: Arch. Surg. **43**: 458, 1941	42	4 yr.	Biliary colic jaundice	Size 20 F catheter 2 inches (5.5 cm.) long	Common duct	Operation	5 yr.	Tube was covered with and occluded by greenish calcareous deposits	Recovery

limits. The thyroid gland was firm to palpation and symmetrically and diffusely enlarged. No bruit was heard. The blood pressure was 140 systolic and 80 diastolic. Well healed right upper rectus and McBurney incisions were present. Some tenderness was noted in the epigastrium and in the right upper quadrant, and there was slight rigidity of the right upper rectus muscle.

The Eagle test of the blood was negative; the hemoglobin value was 84 per cent (Sahli) and the leukocyte count was 10,000, with 82 per cent polymorphonuclear neutrophils. The icteric index was 7.6. On roentgenologic examination a drainage tube was noted in the right upper quadrant of the abdomen and a stone was seen in the pelvis of the left kidney. Gastrointestinal fluoroscopy showed distortion of the second portion of the duodenum suggestive of adhesions in the right upper quadrant of the abdomen. The basal metabolic rate was + 0.6 per cent.

The patient was taken to the operating room; while she was under nitrogen monoxide–ether anesthesia, a right upper paramedian incision was made. The rubber tube was easily felt, and it was grasped through the wall of the common duct with Allis forceps. Then a small longitudinal incision was made in the common duct, and through this the tube fragment was removed. The common duct was about ½ inch (1.27 cm.) in diameter and contained greenish flaky calcareous debris. A size 10 F ureteral catheter was inserted into the common duct and through the ampulla of Vater into the duodenum. About 20 cc. of solution of sodium chloride was injected, and, as none of this fluid regurgitated, it was assumed that the tip of the catheter was in the duodenum. The common duct was irrigated with solution of sodium chloride until no more calcareous material could be evacuated. A new size 12 F rubber catheter was inserted into the common duct with the eye end pointing toward the liver. The tube was sutured to the common duct with plain size 0 gut, and the tube, together with a cigaret drain placed to the site of the opening in the common duct, was brought out through a stab wound in the right flank.

Examination showed the removed piece of tubing to be the end of a size 20 F. catheter about 2 inches (5 cm.) long. The tip had been cut off before the catheter was inserted. The lumen of the tube was completely occluded at both ends by dark greenish calcareous deposits, and the surface of the tube was covered with this material. When the tube was bent, this calcareous material scaled off the surface of the tube in flakes, and on further bending the tube was broken. It was thought that the rubber tube may have acted as a ball valve in the common duct, causing intermittent obstruction.

The postoperative course was marked by elevation of temperature which reached 101 F. every day until the sixth day, when it gradually began to descend to normal. The common duct catheter and the cigaret drain were removed on the fifth and the sutures on the sixth day after operation. Following this, some bile drained, but the drainage gradually diminished, and a few days before the patient was discharged on the twentieth postoperative day, drainage had stopped entirely.

COMMENT

A foreign body may enter the biliary passages (1) from the gastrointestinal tract through the ampulla of Vater, (2) at the time of an

operation on the biliary tract or (3) through a nonoperative wound. The objects found include swabs, thread, bristle, gauze, fruit seeds, steel needles, pieces of wire, a spoon handle, bullets, rubber drains and absorbable and nonabsorbable suture materials. Various parasites, not properly being foreign bodies, are not considered here. In order to avoid leaving portions of rubber drains in the biliary tract, the use of well made new tubing should be insisted on. The tubing used should be such as can be visualized roentgenographically. The table summarizes the pertinent facts concerning cases reported in the literature.

VENOUS THROMBOSIS

EARLY DIAGNOSIS WITH THE AID OF PHLEBOGRAPHY AND ABORTIVE TREATMENT WITH HEPARIN

GUNNAR BAUER, M.D.
MARIESTAD, SWEDEN

Since Jorpes [1] by his work at Karolinska Institutet in Stockholm in 1935 defined the chemical nature of heparin and made this physiologic anticoagulant of Howell available in a pure form, he and his co-workers, as well as other Swedish investigators, have been trying to determine the clinical serviceability of this preparation. Their efforts have been successful. Their results and those of the group in Toronto, Canada, working on the same problem have been summarized in two monographs, by Jorpes [2] and Mason.[3]

One of the most important questions was whether heparin could be used in treating thromboembolic disease. Some valuable work on this problem has been done independently by Crafoord [4] and Crafoord and Jorpes [5] in Stockholm and by Murray and Best in Toronto. In several studies, based on 500 cases, Crafoord has shown that in no instance has postoperative thrombosis appeared in patients who have been subjected to regular treatment with heparin. Such treatment, however, must begin a few hours after operation and continue without a break for five to ten days or longer, with four intravenous injections daily.

Crafoord's studies have shown that in heparin there is available an almost infallible prophylactic against thromboembolism. But valuable though heparin is, practical reasons unfortunately preclude its more general use for prophylaxis. If all patients operated on were treated with heparin, the cost would be prohibitive and the demands on the staff too heavy.

From the General Hospital, Gunnar Bauer, M.D., Head Surgeon.

Read at the joint meeting of the Swedish Association of Surgeons and the Swedish Association of Internal Medicine, Stockholm, Dec. 1, 1940.

1. Jorpes, J. E.: Naturwissenschaften **23**:196, 1935; Biochem. J. **29**:1817, 1935.

2. Jorpes, J. E.: Heparin: Its Chemistry, Physiology and Application in Medicine, New York, Oxford University Press, 1939.

3. Mason, M. F.: Surgery **5**:451 and 618, 1939.

4. Crafoord, C.: Acta chir. Scandinav. **79**:407, 1937; **82**:319, 1939.

5. Crafoord, C., and Jorpes, E.: Heparin as a Prophylactic Against Thromboses, J. A. M. A. **116**:2831 (June 28) 1941.

Nonetheless, heparin seems to be too good and too innocuous an anticoagulant to be abandoned. Perhaps its use might suitably be restricted to the treatment of patients who already have thromboembolism. In such practice, however, another difficulty would be immediately evident, for the experience of Crafoord and others has shown that patients with fully manifest thrombosis are not greatly benefited by treatment with heparin.

The idea then suggested itself that the treatment of thrombosis should begin at a much earlier stage, that is, immediately after the very first manifestations of the disease had appeared. In other words, the treatment should be given not to patients who have thrombosis but to those who are just getting it. Unfortunately, the early and transitory stage of thrombosis evades recognition by ordinary clinical methods. However, by means of phlebography thrombotic conditions in an early stage, in statu nascendi it might be said, may be revealed.

In this paper a short description of this method will be given and the question of its significance for heparin treatment will be considered.

METHOD OF PHLEBOGRAPHIC EXAMINATION

Phlebography, in the sense the term is used here, refers to a method, available for the past two years, which makes it possible to render visible on the x-ray film the deep venous trunks of both the leg and the thigh.

The method used is based on one originated by dos Santos,[6] which has been considerably modified and standardized at the General Hospital of Mariestad. The technic has been fully described in earlier works.[7] It will suffice to state here that with the patient lying on his back a small incision, about 1 cm. in length, is made behind the outer malleolus, and a superficial, rather thick, subcutaneous vein, which is a tributary of the small saphenous vein, is exposed. Into the exposed vein is slowly injected 20 cc. of a 35 per cent solution of perabrodil (diodrast). After about sixty seconds the x-ray film placed under the patient's leg is exposed. The injected vein has numerous anastomoses with the deep veins of the lower part of the leg, and in the roentgenograms of normal patients these veins will therefore show up well filled with the opaque medium. On the other hand, should the deep veins be clogged with thrombotic masses, considerable filling defects or absence of the contrast shadows will be evident on the roentgenogram. Four characteristic phlebograms are reproduced in figure 1.

ORIGIN AND COURSE OF THROMBOSIS

I have made about one hundred and fifty phlebographic examinations, and in my opinion, use of this method casts new light on many phases of the problem of thromboembolism and gives rise to a number of speculations. Most of these I discussed at length in a previous publica-

6. dos Santos, J. C.: J. internat. de chir. **3**:625, 1938.

7. Bauer, G.: (*a*) Nord. med. **8**:1788, 1940; (*b*) Acta chir. Scandinav. (supp. 61) **84**:1, 1940.

tion.[7b] Only two aspects, of special importance for diagnosis and therapy, will be dealt with here.

One result of phlebographic studies is the revised, and probably more correct, view of the origin and inherent nature of thromboembolic disease to which it has given rise. By the term thromboembolic disease is meant, of course, a condition of progressive, or creeping, thrombosis. It thus implies that the thrombotic mass is located in a vein of considerable caliber, that is, a collecting trunk of lower or higher order, and that this thrombotic mass is undergoing continual accretion by the deposition on it of fresh quantities of blood corpuscles and fibrin.

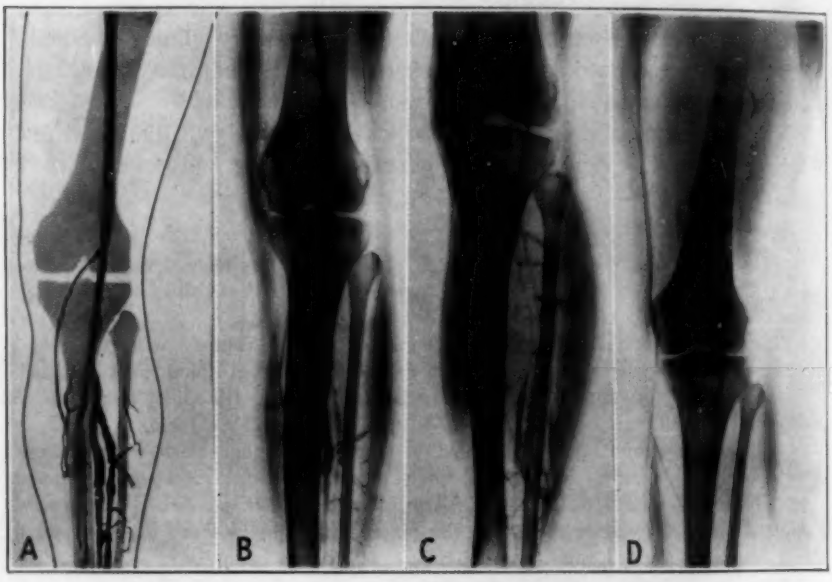

Fig. 1.—*A*, diagrammatic representation of the deep veins usually seen in a normal phlebogram. There is good contrast filling of the femoral, the popliteal, the anterior tibial (in the space between the tibia and the fibula) and the posterior tibial veins. Only a few subcutaneous veins are visible. *B*, normal phlebogram. *C*, recent thrombosis localized to the lower part of the leg. There is no contrast filling of the posterior tibial or of the upper part of the anterior tibial veins. *D*, recent thrombosis of the leg and thigh (phlegmasia alba dolens). There is no contrast filling either of the large, deep venous trunks of the lower part of the leg or of the popliteal or the femoral veins. Only the large saphenous vein and a few superficial veins are visible.

For a long time it was generally thought that the process giving rise to large thrombi started in the large pelvic veins or in the uppermost portion of the femoral vein. During the last decade, however, this view has been undermined. The work of clinicians and pathologists, among

whom may be mentioned Homans,[8] Rössle,[9] Neumann[10] and Frykholm,[11] has shown that the starting point of the process, at any rate in a large percentage of cases, must be in the veins of the lower part of the leg. Phlebography has made a more thorough study of this question possible. I believe that one is now justified in making the statement that almost without exception the thrombotic process has its origin in the deep venous trunks of the lower part of the leg.

By using the phlebographic method and by constantly comparing the roentgenograms with the clinical findings, I have come to the conclusion that the origin and course of thromboembolic disease may be reconstructed as follows:

The whole process starts with a clot, which arises for some unknown reason, protruding from a muscle vein into the lumen of one of the thick venous trunks of the lower part of the leg. It becomes the starting point of a deposition thrombus, which subsequently goes on growing in the direction of the blood stream. Even this first stage can be phlebographically demonstrated, though it will doubtless evade recognition by other methods. In the next stage the large veins of the lower part of the leg are progressively filled, the thrombotic masses in course of time completely filling the lumens and becoming firmly attached to the walls of the vessels. Concurrently, there proceeds a longitudinal growth up through the femoral vein. As a result this vein will eventually contain, freely waving about in the blood stream, an eel-like formation, 40 to 50 cm. long, dark red and with a smooth, slippery surface. This thrombotic structure forms, as it were, a cast of the great vein's lumen, though it does not completely occlude the latter. The wall of the vein is as yet not involved in any way, and the thrombus is anchored only at its lower end, far down in the lower part of the leg.

This condition, which obviously entails great risk of embolism, appears to be commoner than was formerly supposed and, strangely enough, cannot be diagnosed by ordinary clinical methods. The phlebographic examination, however, is a means of unmasking the situation.

In its further development the condition may now follow different lines. The waving thrombus may give rise to an embolus by breaking off at some point and floating up toward the heart. The commonest course, however, is for the thrombus to continue to increase in thickness, so that it entirely blocks the lumen, begins to involve the endothelium of the wall of the vein and becomes firmly fixed to the wall along its

8. Homans, J.: J. internat. de chir. **3**:599, 1938.
9. Rössle, R.: Virchows Arch. f. path. Anat. **300**:180, 1937.
10. Neumann, R.: Virchows Arch. f. path. Anat. **301**:708, 1938.
11. Frykholm, R.: Surg., Gynec. & Obst. **71**:307, 1940.

entire length. The typical picture of phlegmasia alba dolens arises, followed later by one of the several clinical pictures of chronic thrombosis.

In many cases the thrombotic process extends farther and invades the pelvic veins. This occurrence is not associated with clinical symptoms of any considerable prominence, unless there is too great extension, when death may ensue from closure of veins vital to life, for example the renal or mesenteric veins.

Not infrequently the process becomes bilateral. Phlebographic examination shows, however, that in such cases, too, the thrombosis on the other side of the body probably always starts in the lower part of the leg.

DIAGNOSIS OF THROMBOSIS BY PHLEBOGRAPHIC EXAMINATION

This short exposition should make it easier to realize that a surer and earlier diagnosis of thrombosis can be made by phlebographic examination than by the methods hitherto used. It is obviously unnecessary to enumerate here all those elements in the clinical examination which are designed to unmask an early stage of thrombosis. A common feature of them all is that they are unsatisfactory in two types of cases. In the one type the clinical signs are pronounced and incontestible. Phlebographic examination teaches, however, that in cases of this nature the thrombosis is neither recent nor confined to the lower part of the leg. On the contrary, tenderness and swelling do not appear until the thrombotic masses have become firmly attached to the walls of the veins of the lower part of the leg and have produced irritation of the walls, with periphlebitis. And at this stage, of course, there is often present in the femoral vein a large, waving, potentially dangerous thrombus.

In the other type of case the clinical signs of thrombosis are extremely vague and scarcely more than suggestive. In cases of this kind an early stage of thrombosis may be present, but it would be incorrect and misleading to make a diagnosis of thrombosis solely on the basis of such signs. In at least 15 cases of this type I have been able roentgenographically to exclude the presence of thrombosis. In none of these cases did thrombosis subsequently appear.

To insure an early, and at the same time reliable, diagnosis by means of the phlebographic examination, however, one must obviously be exceedingly watchful. Naturally, the examination must not be put off until cleancut clinical symptoms have developed. Moreover, a large number of patients who may be threatened with the thrombosis cannot be phlebographically examined at random. The right procedure must be to keep such patients at all the times under the strictest supervision. Heed must be given to the slightest unexplained rise in the pulse rate

or the temperature, to any unmotivated general restlessness, to the least signs of pulmonary infarction and to the faintest signs of a pathologic condition of the legs, such as a transitory aching in the calf, lasting perhaps only a few hours, a slight change in the color of the skin, a small increase in the firmness of the calf muscles or a tender spot, found only with difficulty, on the back of the lower part of the leg. If phlebographic examination is undertaken in the presence of such signs as these, an accurate diagnosis can usually be obtained in cases in which otherwise one may have merely a faint suspicion that everything is not as it should be. Generally, there will be an absence of opaque filling in one or all of the deep veins of the lower part of the leg, which not only insures the diagnosis but provides objective photographic evidence of the condition. On the other hand, if a normal roentgenogram is obtained—this has occurred in about one fifth of my cases—the possibility of thrombosis is excluded and also all false conclusions respecting the results of therapy instituted on mere suspicion of thrombosis.

TREATMENT OF THROMBOSIS

If it is considered an established fact that the phlebographic examination makes possible the diagnosis of thrombotic disease in its earliest stages, one requisite for successful treatment with heparin has been attained. The other must consist in determining whether a beneficial effect arises from the treatment in cases of the early stages of the disease discovered by such examination.

Theoretically, of course, benefit should ensue. According to what is known, heparin has no direct effect on thrombotic masses which have already entirely filled the vascular lumen and begun to involve the wall. On the other hand, the drug is able to prevent a spread of such masses. Within the thrombosed lower part of a leg changes may be present of such a type that no great effect on them can be expected from treatment with heparin. This, however, is of no consequence, for according to my experience obliteration of the deep veins has no noteworthy significance either for the present or for the future if the process is confined to the lower part of the leg. On the other hand, treatment with heparin can save the veins of the thigh from being occluded. If on the roentgenogram the femoral vein is well defined, there are no thrombotic masses in it and the immediate institution of heparin treatment ought to, and does, prevent the subsequent appearance of such masses.

Treatment of Thrombosis Without the Use of Heparin.—When the practical results of heparin treatment are to be judged, the first step is to get a clear idea of what is the usual fate of patients with thrombosis if such treatment is not undertaken. Relevant to this question is the

material I have at my disposal from 32 cases in which an early stage of thrombosis of the lower part of the leg was phlebographically demonstrated. The patients received no heparin, but in other respects they were treated in the generally accepted way: with elevation of the legs, heat and, in some cases, blocking of the lumbar sympathetic ganglions with procaine hydrochloride. In spite of this therapy the thrombotic process remained localized to the lower part of the leg in only 25 per cent of the cases. In 75 per cent the femoral vein was affected and pronounced phlegmasia alba dolens followed. In 31 per cent the thrombosis became bilateral. In 16 per cent there was extension of the process to the great pelvic veins as well, and in 1 case death ensued on account of thrombosis of the superior mesenteric vein. Further, in

Comparative Data for Cases of an Early Stage of Thrombosis Localized to the Lower Part of the Leg in Which Heparin Was Used and for Similar Cases in Which It Was Not Used.

	Cases in Which Heparin Was Not Used	Cases in Which Heparin Was Used
Total number of cases	32	21
Cases in which thrombosis remained localized to the lower part of the leg	8 (25%)	21 (100%)
Cases in which the thrombotic process spread	24 (75%)	..
Spread to the thigh, phlegmasia alba dolens	24	..
Undoubted spread to pelvic veins	5	..
Thrombosis of mesenteric vein	1	..
Pulmonary infarction	8	..
Pulmonary embolism	3	..
Thrombosis of the other leg	10	..
Cases in which patient died of complication of thrombosis	2 (6%)	..
Average confinement to bed after diagnosis of thrombosis, days	43	6.7

34 per cent of the cases there were larger or smaller pulmonary infarcts and in 1 case fatal pulmonary embolism. Probably the figure for the latter complications would have been still higher if in cases in which the prognosis appeared especially threatening ligation of the femoral vein had not been employed to stop further advance of the process (table). Thus, great immediate risks, long confinement to bed and considerable later discomfort threaten the great majority of patients once they have beginning thrombosis of the lower part of the leg.

Abortive Treatment of Thrombosis with Heparin.—In striking contrast are the results obtained after the summer of 1940, when in cases of exactly the same type my associates and I began to use heparin. The number of cases observed to date is small (21), but there have been no failures or dubious results in this series. Without exception the temperature and pulse curves, which were commencing to rise, have become normal again within two to four days, and within the same space of time nearly all tenderness on palpation of the lower part of the

leg and all swelling and aching have vanished. The patients have usually been able to get up after another couple of days, provided the primary disease did not prolong their stay in bed. Spread of the thrombosis has not been observed in any case, nor have there been any pulmonary infarcts. As a rule, the patients required administration of heparin for only three to five days and after this time could be regarded as cured. Hence, in these cases, there is some reason for speaking of an abortive treatment of the thrombotic disease (fig. 2).

Dosage: The question of the dosage of heparin to be used in such cases obviously can be answered only after there has been much experience. The daily quantity given undoubtedly ought to be fairly large. At present, I can merely say that in several cases I have succeeded in achieving abortion of the process with such small daily doses as 150 to 200 mg. given in three or four intravenous injections, but since conferring with Jorpes I have seldom given less than 300 mg. daily. Usually the patients receive 100 mg. intravenously three times a day. The first dose is often increased to 125 or, at most, 150 mg. The total quantity employed is between 900 and 1,300 mg. of the ordinary commercial heparin. With this dosage there have been no failures among the cases of thrombosis in which a diagnosis was made early.

Duration of Treatment: A further question to be answered is how many days the heparin treatment is to be continued. I have gradually come to the conclusion that treatment can cease as soon as the pulse curve has become almost normal and the temperature has dropped to within a few tenths of a degree of normal. On the other hand, there is no need to wait until all traces of tenderness on palpation have disappeared. As a rule, it has not been necessary for me to give heparin more than three to five days in cases in which the treatment was abortive. A day or so later the patient is ready to get up.

Treatment of Later Stages of Thrombosis with Heparin.—What has been said refers to what may be called abortive treatment. The use of heparin, however, may well be adopted in certain other circumstances. One must doubtless always count on not being able in all cases to reach a diagnosis as early as is desirable. The onset of thrombotic disease may be either so insidious and imperceptible or so sudden that on the phlebogram even the shadow of the femoral vein will be absent, showing that there is a thrombus in that vein. Ought one to give heparin in such cases?

According to my experience, in the later stages thrombosis may be divided into two types: 1. The thrombus in the femoral vein may be so recent that it is still loosely waving about in the vein. Clinically, this stage is characterized by absence of tenderness on palpation along the course of the vein. On phlebographic examination an extremely small amount of contrast medium may be seen in the femoral vein, in the

form of a mantle shadow, or nothing at all may be visible. In such cases treatment with large doses of heparin should be followed. There is the possibility that the thrombus, which will cease to grow, can be

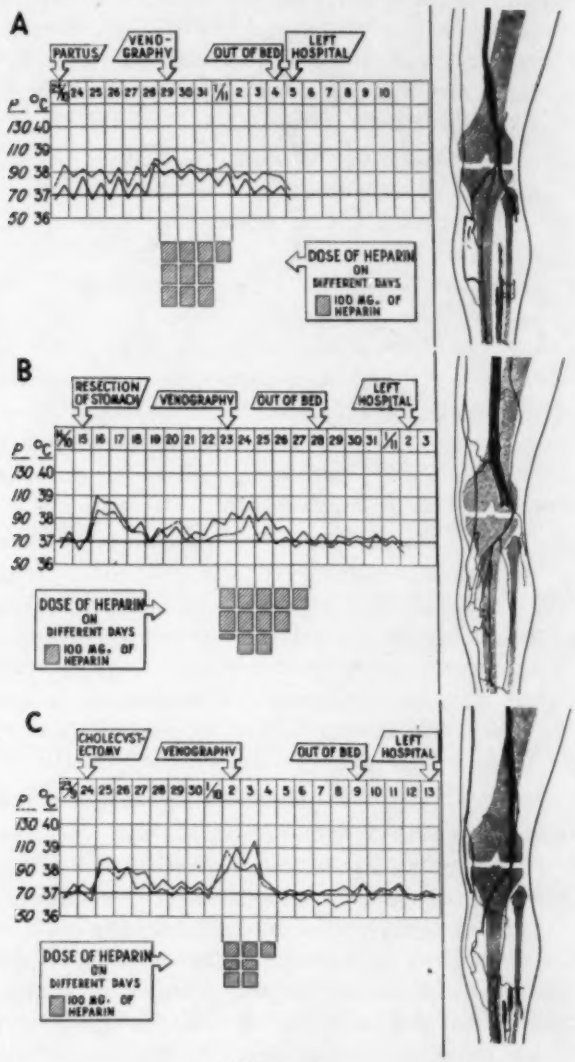

Figure 2

(See legend on opposite page)

dissolved by fibrinolysis in the blood and will disappear. I have a case in which the photographic records seem to indicate that such a dissolution of a thick thrombus took place after a few days of treatment with heparin. Thus, in this type of case, too, the use of heparin serves as a form of

abortive treatment. In such cases the treatment naturally must be continued considerably longer than in the cases of recent thrombosis.

2. Marked tenderness on palpation over the femoral vein and the presence of true phlegmasia alba dolens signify that the thrombus in the femoral vein is already firmly adherent to the wall. No effect from the administration of heparin can therefore be expected in the thrombosed leg. It nevertheless appears to be a logical procedure to introduce such therapy with a view to preventing the thrombosis from becoming bilateral, spreading to the pelvic veins or giving rise to pulmonary complications. On this point my experience is not sufficient to allow of any conclusions.

SUMMARY

For successfully combating thromboembolic disease two measures are necessary: early diagnosis and immediate energetic treatment with heparin.

Phlebography permits of an earlier diagnosis than any other known method. With its aid the first manifestations of the disease in the lower part of the leg can be revealed.

EXPLANATION OF FIGURE 2

Fig. 2.—*A*, abortive treatment with heparin in a case of thrombosis of the left leg. There was a rise in the temperature and pulse curves on the sixth day after a normal delivery. Examination disclosed nothing pathologic except slight tenderness on palpation over the back of the left calf, at the line dividing the top and middle thirds. The phlebogram shows defective contrast filling of the deep venous trunks of the lower part of the leg. The thrombosis is in an early stage and still localized to the lower part of the leg. Immediate treatment with heparin was begun. Three 100 mg. doses were given intravenously for three days and one dose on the fourth day, making a total of 1,000 mg. in four days. On the fourth day all tenderness and swelling were gone, and the pulse and temperature were almost normal. The patient got up on the sixth day and left the hospital the next day. Confinement to bed after diagnosis of the thrombosis was for six days instead of for six weeks, the average period in cases of thrombosis. *B*, abortive treatment with heparin of postoperative thrombosis of the right leg. On the eighth day after operation, there were a rise in temperature and slight swelling of the lower part of the right leg with slight tenderness of the calf. The phlebogram shows thrombosis of all the deep venous trunks of the lower part of the leg and what is probably the head of a waving thrombus in the popliteal vein. Intravenous administration of heparin was begun immediately. On the first day two doses, 125 mg. and 100 mg., were given and on the following three days three 100 mg. doses were administered, or a total of 1,125 mg. in five days. The temperature and pulse rate fell quickly, and the swelling and tenderness receded. The patient got up after five days. The danger of phlegmasia alba dolens or even of pulmonary embolism was averted. *C*, abortive treatment with heparin of postoperative thrombosis of the left leg. In this case somewhat less heparin was given, a total of 475 mg. being administered in three days. The same good result was attained as in the cases previously described.

If in this stage regular treatment with heparin is started, almost ideal results can be expected, for the whole disease often takes an abortive course.

In 21 cases in which the diagnosis of an early stage of thrombosis in the lower part of the leg was confirmed by phlebographic examination, the patient was treated with heparin, 100 mg. three times daily for three to five days. All of the patients recovered and were ambulatory in a few days.

In 32 similar cases in which treatment with heparin was not used, 2 patients died, 3 had pulmonary embolism and 8 pulmonary infarct and in 24 the thrombosis spread to the femoral veins. The average length of confinement to bed was forty-three days.

CONGENITAL LUMBOSACRAL DEFECT

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AND

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The causation and the anatomy of lumbosacral defect have not been well studied, and the assumption is generally made that nothing can be done about the condition. Many of the unfortunate persons with this deformity are of normal mentality. At least 2 persons described in the medical literature, while apparently completely lacking a sacrum, have gone through two pregnancies each. An understanding of their difficulty should be of interest.

The literature on this anomaly lists 41 cases. Since they have been adequately reviewed in recent years, we merely cite the reviews,[1] together with a few isolated cases, and contribute a case that came to our attention at the Children's Hospital in Galveston.

REPORT OF CASES

CASE 1.—A bright looking 9 year old boy was admitted to the orthopedic service by one of us (N. D.) in November 1940 (fig. 1). He was able to sit up and drag himself about by the use of his arms but had no use of his voluntary muscles below the thorax. The head appeared moderately hydrocephalic. The neck was short and the chest large, barrel shaped and muscular. The thoracic spine was lordotic above and kyphotic below. Spinous processes were missing on and below the twelfth thoracic vertebra. The abdomen tapered abruptly. The sacrum could not be palpated, and the pelvis was narrow. The legs were flexed sharply on the thighs, the heels touched, and the soles faced upward and inward. A web of skin extended from the posterior surface of the thighs to the calves, obliterating the popliteal spaces. The symphysis pubis was present, and both the anus and the genitalia appeared normal.

The heart and lungs appeared to function normally. Incontinence of urine and feces was present. Muscle was absent or completely atrophied in the limbs, and no reflexes were obtained. Cutaneous sensation was normal. While he felt neither pain nor discomfort from his condition, pain could be elicited on vigorous manipu-

From the University of Texas School of Medicine.

1. Hamsa, W. R.: Congenital Absence of Sacrum, Arch. Surg. **30**:657-666 (April) 1935. Girard, P. M.: Congenital Absence of Sacrum, J. Bone & Joint Surg. **17**:1062-1064 (Oct.) 1935. Zeligs, I. M.: Congenital Absence of Sacrum, Arch. Surg. **41**:1220-1228 (Nov.) 1940.

Fig. 1.—A 9 year old boy with congenital lumbosacral defect.

Fig. 2.—Roentgenogram of pelvic defect showing medial articulation of the twelfth ribs and of the iliac crests. Lumbosacral vertebrae are missing.

lation. The skin showed no trophic disturbance. The result of a Wassermann test was negative.

A roentgen examination was made by one of us (J. C. R.). The large cranial vault showed no widened sutures or evidence of pressure on the sella turcica. The spines from the fifth cervical to the second thoracic vertebra were bifid. The body of the twelfth thoracic vertebra was absent, yet the ribs, derived from its transverse processes in early development, nearly articulated across the midline (fig. 2). All vertebrae below this were missing or at least did not show any ossified remnants. The iliac bones articulated with each other. The limb bones were normal except for a small defect of the right fibula.

This boy came from a family of 8 members, all of whom were normal. His deformity had been present since birth. It was felt that nothing could be done for him, and after examination he went home.

CASE 2.—In 1932 we obtained locally a 60 mm. fetus presenting the same external picture as the boy just described. Nothing was known of the parentage.

Fig. 3.—Lumbosacral defect in a 60 mm. fetus.

The fetus showed a normally developed head and trunk to the middle lumbar region, but from there it quickly shrunk to a size suitable to a much smaller fetus, with all parts apparently well formed (fig. 3). The skin showed some edema but no vascular congestion.

A dissection of the back showed normal development of all the extensor muscles and vertebrae back to the last thoracic segment. In the lumbar region the muscles continued intact to the level of the constriction. At this level all muscles except the extensors showed traumatic distortion, and muscles lateral to the centrums were ruptured, as the lower lumbar wall was telescoped into the upper wall for a distance of one segment. The defect continued ventrally to the umbilical cord. Below the fold all muscle again became normal but reduced in volume.

Serial transverse sections were prepared from upper lumbar levels downward (fig. 4). The first, second and third vertebral arches showed progressive spina bifida similar to the normal arches of the lower sacral segments. This shallow

trough continued through the lumbar, sacral and coccygeal regions, all segments being present in cartilage. The pelvic girdle and limb cartilages were normal. The fourth lumbar centrum began normally but tapered out caudally to a thin wedge lacking perichondrium. Ventral to the fourth lumbar centrum lay the fifth. It started cranially as a long irregular wedge without perichondrium and became normal caudally. Its vertebral arch was sheared off on one side and lay wedged into the vertebral notch of the one above. On the other side it pressed the centrum above it, causing a kink in the vertebral canal and torsion of the

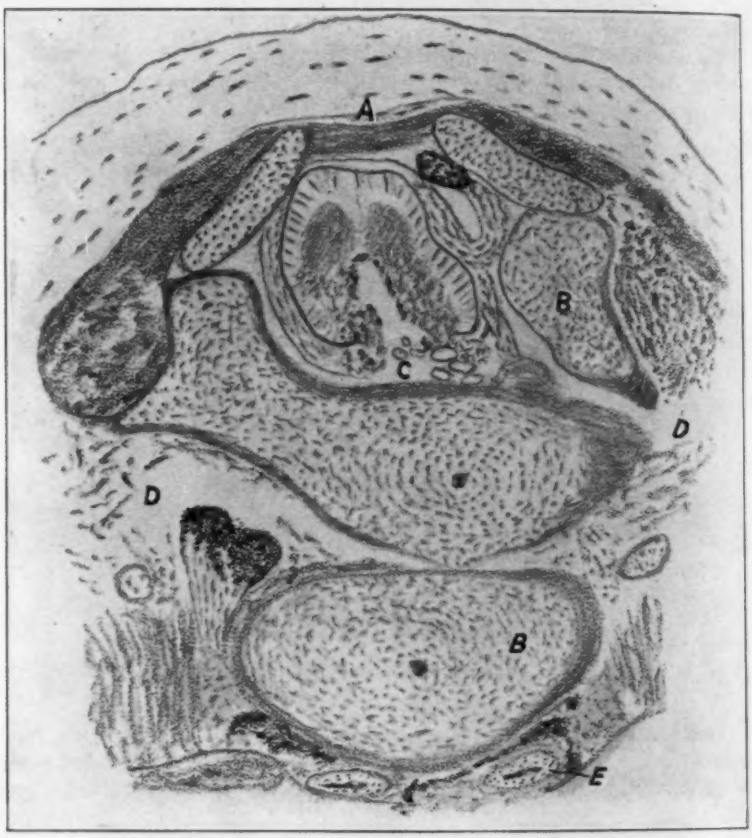

Fig. 4.—Section of the back of a 60 mm. fetus through the level of the lumbosacral defect. *A* is the spina bifida; *B* is the fifth lumbar centrum and displaced arch; *C* is the beginning of the ventral defect of the spinal cord; *D* is the level of rupture of muscle and nerves; *E* indicates the compressed common iliac arteries.

spinal cord. The sacral centrums lay in line with that of the fifth lumbar. Each centrum contained a segment of the notochord.

The spinal cord filled the open trough nearly to the end of the vertebral column and was so thick that it rose above the crests of the spread arches. In the upper lumbar levels it showed a patchy ependyma even where the rest of the

section was normal. At the level of the fault, the floor of the canal dropped, and the dura attached to the fifth vertebra at the foramens pulled downward on the cord. The wedgelike end of the fourth lumbar centrum spread the ventral half of the cord and penetrated into the neural canal. Immediately below this the ventral gray matter and lateral and ventral funiculi were completely disintegrated, not by atrophy or necrosis but by trauma. The scattered cells still stained normally.

The aorta bifurcated just above the fault line after the mesenteric and renal arteries branched off. Under the last lumbar vertebral body the common iliac arteries were compressed almost to obliteration, though under full arterial pressure they had apparently functioned to some extent. Most of the blood here was destined for the placenta, and this compression may easily have been the cause of death. All viscera were perfectly developed.

An explanation of this developmental defect goes back to a stage when the embryo was 4 to 15 mm. in length. During this period the sclerotomes are formed and begin to chondrify. There was evidence of developmental arrest of the arches below the thorax, even though other segmental mesodermal derivatives were normal. From some unknown cause the plane separating the fourth and fifth lumbar segments was neither vertical to the axis nor strictly transverse. No difficulty was experienced until the large extensor muscles of the back began to contract. Under the strain, the vertebrae were displaced along the fault plane, perichondrium was gradually stripped, the umbilical vessels were compressed, and the spinal cord was broken. The process was gradual, including limitation of blood to the legs and loss of cerebral control of the voluntary musculature. This, of course, includes the striated sphincters of the anus and urethra. It in no wise affected the smooth muscles of the gut or urogenital tract. The sympathetic chain was intact. The dorsal roots and spinal ganglions were intact, except for one pair, together with the dorsal funiculi and the dorsal half of the gray matter. In this way afferent tracts were preserved in part, even pain and temperature fibers for a couple of segments below the injury.

COMMENT

It is probable that this explanation when adapted to various levels, various angles or degrees of depression and different intervals of time may be applied to the lumbosacral defects described in the literature. In all of the reported cases, the afferent tracts were fairly well preserved, while the voluntary motor controls were impaired or missing. There was incontinence of feces and urine. The pelvic girdle developed without vertebral support. Spina bifida and other vertebral defects were commonly associated with vertebral termination, generally in the lumbar region. From a developmental standpoint it seemed impossible to have complete agenesis of somites or of any part of them, because both epaxial and hypaxial myotomes were developed. Any asymmetric segmental development of a single somite would produce an oblique intervertebral plane. Since the notochord was present in thoracic levels, it must have been continuous with the primitive knot from which it originated. If sclerotomes had not developed, the neural crest would not have been

separated into ganglions, and the sympathetic chain, which became separated ventrally from it, could hardly have been formed. Suppression of primordiums originally present offers a more reasonable explanation. The idea that the defect was purely traumatic and not based on an embryonic fault is not true. It does not account for the peculiar angle of the intervertebral plane or for the spina bifida generally present. A failure of the cartilaginous elements below the defect to ossify would present itself in a child as lack of skeletal support and would not show in a roentgenogram. If the final compression did not occur until the spinal cord was drawn well up into the vertebral canal, the injury would not involve so many neural segments so completely. The apparent lack of somatic muscles may well be due to failure of these muscles to develop beyond a fetal stage for lack of functioning reflex paths.

In conclusion, it seems possible that congenital lumbosacral defect may be traced back to a simple vertebral defect at the stage of chondrification or the later stage of ossification. This simple defect during the development of extensor functions of the back may be aggravated to present a picture of complete somatic dysfunction or atrophy below the level of the fault.

SUMMARY

Congenital absence of lumbar and sacral vertebrae is compatible with life and with considerable visceral function. It is associated with other skeletal anomalies, with loss of somatic motor controls below the upper level of the anomaly, with preservation of afferent paths and with general atrophy or undevelopment of muscle in the lower part of the body and limbs. It is traced back to the stage at which vertebral primordia are laid down and consists in faulty intervertebral articular planes. The extensor muscles dislocate the centrums along an oblique plane, the cartilages thereby compressing the aorta, rupturing muscles and some nerves and compressing or destroying part of the ventral half of the cord.

A 9 year old boy is compared with a 60 mm. fetus, both having similar defects.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1940

THE FIRST OF A NEW SERIES OF REVIEWS WHICH WILL BE PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

PREFACE

Realizing the value of a more comprehensive review of the orthopedic literature than was being published, the American Academy of Orthopaedic Surgeons, through its executive committee, decided to sponsor a new "Progress in Orthopedic Surgery" and authorized the editorial committee to proceed in its preparation for the literature of 1940. An editorial board of twenty-three orthopedic surgeons representing twenty different centers was appointed by the president of the Academy, with the chairman of the editorial committee as the chairman of this editorial board. The members of the board are as follows:

Dr. LeRoy C. Abbott, San Francisco, Professor of Orthopedic Surgery, University of California Medical School

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Dr. Frank D. Dickson, Kansas City, Mo., Chief of Orthopedic Service, St. Luke's, Kansas City General and Wheatley-Provident Hospitals, Professor of Clinical Surgery, University of Kansas School of Medicine

Dr. Rex L. Diveley, Kansas City, Mo., Associate Chief of Orthopedic Service, St. Luke's, Kansas City General and Wheatley-Provident Hospitals

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Dr. I. William Nachlas, Baltimore, Associate in Orthopedic Surgery, Johns Hopkins University School of Medicine

Dr. Winthrop M. Phelps, Baltimore, Medical Director, Children's Rehabilitation Institute; formerly Professor of Orthopedic Surgery at Yale University School of Medicine

Dr. Robert D. Schrock, Omaha, Professor of Orthopedic Surgery, University of Nebraska College of Medicine

Dr. Alfred R. Shands Jr., Wilmington, Del., Chairman of the Editorial Board, Medical Director of the Alfred I. duPont Institute of the Nemours Foundation; Visiting Professor of Orthopedic Surgery, University of Pennsylvania School of Medicine

Dr. Alan DeForest Smith, New York, Surgeon in Chief, New York Orthopedic Hospital; Clinical Professor of Orthopedic Surgery, Columbia University College of Physicians and Surgeons

Dr. J. Spencer Speed, Memphis, Tenn., Surgeon in Chief, Willis C. Campbell Clinic; Professor of Orthopedic Surgery, University of Tennessee College of Medicine

Dr. Arthur Steindler, Iowa City, Professor and Head of Department of Orthopedic Surgery, State University of Iowa College of Medicine

Dr. Loring T. Swaim, Boston, formerly Chief of Medical Staff, Robert Breck Brigham Hospital; Instructor in Orthopedic Surgery, Harvard Medical School

Dr. J. Warren White, Greenville, S. C., Surgeon in Chief, Shriners' Hospital for Crippled Children

Dr. Philip D. Wilson, New York, Surgeon in Chief, Hospital for Ruptured and Crippled; Clinical Professor of Orthopedic Surgery, Columbia University College of Physicians and Surgeons

The chairman of the editorial board divided orthopedic surgery into 20 subjects, the complete list of which was published in the July issue of the ARCHIVES OF SURGERY (p. 168). Each editor was assigned a subject, to which in most instances either he or the group he represents has made outstanding contributions in the past. The titles of 1,794 articles of orthopedic interest were selected from the *Quarterly Cumulative Index Medicus* for 1940. These were then grouped according to subject as accurately as possible from the titles and sent to the proper editor for review. Each editor was instructed to report only on articles which appeared to represent definite progress or to contain information of unusual interest. The total number of articles reviewed in the final report is 687. It is to be regretted that owing to the European war it has been impossible to obtain many of the foreign publications.

Some subjects, such as "Fresh Fractures and Dislocations," have a more voluminous literature than others; accordingly, these sections are longer. An attempt has been made to adopt a uniform style in the presentation of the material. However, in this first publication, with 20 sections being prepared for the first time in as many different centers, this has been only partly accomplished. Some sections have more editorial comments than others. These are the reactions of the individual editors to the articles being reviewed. If the reader or the author

of any article does not agree with the editorial comment, the editorial committee hopes that he will think of the remark as only one man's impression and as in no way representing the opinion of the entire editorial board.

In the preparation of the material, the following orthopedic surgeons acted as assistants to the editorial board:

For Dr. Abbott:	Dr. J. B. DeC. M. Saunders, San Francisco
	Dr. F. C. Bost, San Francisco
	Dr. K. O. Haldeman, San Francisco
	Dr. R. Soto-Hall, San Francisco
For Dr. Colonna:	Dr. W. A. Klein, Oklahoma City
For Dr. Ghormley:	Dr. H. H. Young, Rochester, Minn.
For Dr. Shands:	Dr. G. Newton Boice, Wilmington, Del.
	Dr. W. Richard Ferguson, Wilmington, Del.
	Dr. W. B. Sheppard, Wilmington, Del.
	Dr. Raymond P. Thornhill, Wilmington, Del.
For Dr. Smith:	Orthopedic staff of New York Orthopædic Dispensary and Hospital
For Dr. Steindler:	Dr. J. L. Marxer, Iowa City
	Dr. L. A. Williams, Iowa City
	Dr. M. Rosenbusch, Iowa City
	Dr. L. J. Barron, Iowa City
	Dr. A. L. Freedman, Iowa City
	Dr. J. S. Mule, Iowa City
	Dr. G. Miyakawa, Iowa City
	Dr. T. J. Greteman, Iowa City
For Dr. Swaim:	Dr. George J. Baer, Boston
	Dr. John P. Stump, New York
For translation of Latin-American articles:	Dr. Alberto Inclán, Habana, Cuba

The ARCHIVES OF SURGERY kindly agreed to allow this new "Progress in Orthopedic Surgery" to replace the old "Progress," published for many years in its pages. It is sincerely hoped that this "Progress" during its first year may receive the approval and good will of its readers and prove to be a publication of great usefulness to all interested in the problems of orthopedic surgery.

(Signed) The Editorial Committee of the
American Academy of Orthopaedic Surgeons.

E. BISHOP MUMFORD, M.D.

REX L. DIVELEY, M.D.

A. R. SHANDS JR., M.D., Chairman.

I. CONGENITAL DEFORMITIES

General Considerations.—The study of human fetal malformations includes not only the gross anomalies which are called monsters but also every possible disturbance of structural and functional development. Teratology is the name given this science, and according to Savage and Dorman [1] in an interesting review of the subject, it is derived from the Greek τέρας, meaning monster. "Congenital" means that the anomalies were present at birth; "hereditary," that they were received through the inheritance of defects of ancestors.

Mall taught that monsters were produced by external influences on normal ova. Piette [2] gives another explanation. He states that it appears possible that most spontaneous abortions, stillbirths, monstrosities and malformations are due to the fertilization of dying ova, which have apparently a short span of life.

He writes:

> It seems possible that a monstrosity or a malformation is the *result of the fertilization of a dying ovum* by a normal spermatozoon or, less likely, the result of the fertilization of a healthy egg by a dying spermatozoon. The first possibility appears more likely, because the ovum, according to the prevailing current concept, has a very limited span of life, some forty-eight hours or less, whereas the life span of a spermatozoon is seventy-four hours. Watching any protozoon die under a microscope—an ameba or a flagellate, for instance—one notices that it does not die at once and in all parts at the same time. Some parts survive much longer than the others. If, therefore, an egg is impregnated by a spermatozoon at, say, forty hours after extrusion, when it is on its last—is almost dead—a grave malformation may result. If the egg is but slightly damaged by the process of its rapidly approaching senility one may expect a slight malformation of one part of the body of the fetus. If the ovum was all but dead at the time of fertilization one might expect not only a malformation but a dead fetus unable even to go through the stages of intrauterine development.

Savage and Dorman [1] report that in 8,365 deliveries in the department of obstetrics of the University of Maryland School of Medicine only 41 (0.49 per cent) anomalies of the types which are usually seen by the orthopedic surgeon were observed. Thirty-two of these were examples of polydactylism, and 9, of clubfoot.

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1. Savage, J. E., and Dorman, J. W.: Congenital Anomalies, Bull. School Med. Univ. Maryland **25**:23-30 (July) 1940.

2. Piette, E. C.: Possible Cause of Malformations and Spontaneous Abortions, Illinois M. J. **77**:375-376 (April) 1940.

The Klippel-Feil Syndrome.—A complete review of articles on congenital synostosis of the cervicothoracic vertebrae (the Klippel-Feil syndrome) has been made by Rechtman and Horwitz.[3] After summarizing about 83 articles, they report 3 cases. The syndrome is characterized first by shortness of the neck. The head appears to be directly implanted on the trunk. The neck is broad, and the chin approximates and may even rest on the sternum. Occasionally, the trapezial muscles stretch winglike from the mastoid processes to the shoulders, suggesting the name of pterygium colli or web neck. In addition, the syndrome is characterized by low implantation of the hair line and limitation of movements of the head and neck. These movements are painless, the deficiency being purely mechanical. The secondary characteristics are: (1) scoliosis or kyphoscoliosis, (2) elevation of the scapulas, (3) descent of the nipples of the breast and (4) disproportion between the length of the extremities and the trunk, which gives the patient an almost simian appearance. These characteristics may occur in whole or in part and with varying degrees of intensity.

From the standpoint of pathologic anatomy the main changes in the cases described by Feil were a reduction in the number of cervical vertebrae, which were fused in whole or in part, the presence of a superior cervical spina bifida and an elevation of the thoracic cage with formation of a cervical thorax, which was more or less developed. The diagnosis is easily confirmed by roentgenography, which is necessary to rule out more serious lesions of the neck.

There is no therapy for the cervical deformity itself. The prognosis is good. Associated deformities, such as scoliosis, torticollis, clubfoot and clubhand, should be corrected.

Cleidocranial Dysostosis.—This may be defined as a congenital anomaly which may or may not be hereditary and which consists of a material defect in the clavicles without attempted repair and a large brachycephalic skull with a tendency for the fontanels and sutures to remain patent. Such a description is given by Miles,[4] who has made a careful review of the literature and has added 6 cases of his own, 5 of which were in the same family.

Meckel published in 1760 what is probably the first record of a human being born without clavicles. Pierre Marie and Paul Sainton

3. Rechtman, A. M., and Horwitz, M. T.: Congenital Synostosis of the Cervicothoracic Vertebrae (Klippel-Feil Syndrome), Am. J. Roentgenol. **43**:66-73 (Jan.) 1940.

4. Miles, P. W.: Cleidocranial Dysostosis: Survey of Six New Cases and One Hundred and Twenty-Six from Literature, J. Kansas M. Soc. **41**:462-468 (Nov.) 1940.

in 1898 named the condition *la dysostose cléidocranienne héréditaire* and listed four characteristics: aplasia of the clavicles, brachycephaly, persistent fontanels and hereditary transmission. Miles [4] says that the incidence of this rare condition is not evidently increasing and presents few or no medical problems. When a patient with this condition consults a doctor, however, he asks many questions. "It is certainly comforting to know," writes Miles, "that anticipated children will not be abnormal mentally and that they have a 50 per cent chance to be normal physically." In his review of 132 cases he found that 47 per cent of these cases were familial, the deformity appearing in two or three generations, nearly all members of which were affected. Fifty-three per cent were isolated nonhereditary cases.

Marshall and Wulff [5] call attention to the deformity of the pelvis due to cleidocranial dysostosis. This anomaly is characterized by delayed or incomplete ossification of the skeleton, usually affecting most of the bones formed from membrane. They observed a mother and her child who had many deformities due to this dysostosis. The mother had a deformed pelvis, and the paper deals with the obstetric problem which the distortion presented. [ED. NOTE: Pelvic deformity is seldom if ever thought of in connection with cleidocranial dysostosis.]

Absence of the Pectoral Muscles.—Brown and McDowell [6] say that more than 300 cases of congenital absence of the pectoral muscles have been reported but that the true incidence of the lesion is unknown because the deformity is often not obvious and is discovered only by careful examination of the area about the shoulder. The lesion is usually not disabling. They report 2 cases in which this deformity was found associated with syndactylism.

Deformity of the Upper Extremity.—Stein and Bettmann [7] present a rare malformation of the arm in a woman of 52. She had a giant scapula, a double humerus, two radiuses, three ulnas and three hands with sixteen fingers. A similar case cannot be found in the literature. The three hands could perform useful tasks alone or in combination, since they had muscle groups of normal shape and number. The hands could be flexed and extended independently, making all known combinations of flexion and extension possible.

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5. Marshall, C. J., and Wulff, B. I.: Deformed Pelvis Due to Cleidocranial Dysostosis, Am. J. Obst. & Gynec. **39**:136-137 (Jan.) 1940.

6. Brown, J. B., and McDowell, F.: Syndactylism with Absence of the Pectoralis Major, Surgery **7**:599-601 (April) 1940.

7. Stein, H. C., and Bettmann, E. H.: Rare Malformation of Arm: Double Humerus with Three Hands and Sixteen Fingers, Am. J. Surg. **50**:336-343 (Nov.) 1940.

Congenital Dislocation of the Elbow.—Mauck and Butterworth [8] report 2 cases of bilateral congenital dislocation of the head of the radius. This is a relatively rare condition. They operated on one of the arms to reduce the dislocation and tried to hold the head of the radius in position with a sling of fascia lata round the radial neck. When the elbow was extended during the operation, the fascia lata was torn. The head could not be held in position because it was convex and the coronoid fossa ill formed. The head of the radius was removed. They conclude that the pathologic condition is such that any operation other than removal of the head is not satisfactory.

Syndactylism.—Snedecor and Harryman [9] report the Jackson White family to confirm the statement of Edwards that syndactylism is a stigma of degeneration occurring in persons of weakened intelligence. This family is a mixture of English, Hessian, Indian and Negro. During the Revolution an English sea captain named Jackson was commissioned to bring over a cargo of women for the Hessian soldiers garrisoned in New York. In the course of events he bought or shanghaied a boatload of female derelicts off the streets of London and later added some Negresses from the West Indies. After the war these with some abandoned Hessians and Indians were driven to the Ramapo Mountains, where they lived undisturbed by civilization for a hundred and fifty years. Syndactylism and polydactylism have been traced back for four generations. They conclude that the contributing factors causing this defect to appear were inbreeding, low intelligence, dietary deficiencies and poverty in an outcast environment for many generations. This condition occurred in over 50 per cent of the progeny.

Haas [10] reports 2 cases of complete bilateral syndactylism. The patients were brother and sister. The mother had had severe syndactylism of both hands. These deformities are congenital and represent an atavistic trait. Restoration of six fingers with their corresponding metacarpal bones was secured on both hands in the patient whose case is described in detail.

Seventy-three patients with congenital webbing of the fingers have been studied by MacCollum.[11] In discussing the anomaly embryologically he states that between the sixth and the seventh week of fetal

8. Mauck, H. P., and Butterworth, R. D.: Two Cases of Bilateral Congenital Dislocation of the Head of the Radius, J. A. M. A. **114**:2542-2543 (June 29) 1940.

9. Snedecor, S. T., and Harryman, W. K.: Surgical Problems in Hereditary Polydactylism and Syndactylism, J. M. Soc. New Jersey **37**:443-449 (Sept.) 1940.

10. Haas, S. L.: Bilateral Complete Syndactylism of All Fingers, Am. J. Surg. **50**:363-366 (Nov.) 1940.

11. MacCollum, D. W.: Webbed Fingers, Surg., Gynec. & Obst. **71**:782-789 (Dec.) 1940.

life the finger buds grow more rapidly than any other portion of the appendage. Because the growth of the finger buds is so much more rapid than the tissue between them, the webs become less and less marked until finally the only remnants are the webs that exist on the palmar surface of the normal hand. If there is a temporary arrest in development during the seventh or eighth week of fetal life, this disproportionate rate of growth will not occur. It is then quite possible for two or more fingers to be momentarily retarded in growth and to remain united by their webs. Later in fetal life, growth both of the finger buds and of the webs between them takes place at an even rate so that at birth, even though the fingers may have attained proper length, the webs will still be present and of the same length as the fingers.

The sex ratio in MacCollum's series was the same as in most others —66 per cent males to 34 per cent females. Forty-eight per cent showed involvement of both hands. [ED. NOTE: This percentage is the same as for congenital clubfoot.]

He has found that the best time for operation when the web holds the fingers tightly together is between 2 and 5 years. To operate on a baby with tightly fused fingers in the first two years of life exacts the ultimate of patience from the surgeon both during the operation and later as he daily tries to bandage tiny wriggling fingers. Frequently a successful operative result is ruined by lack of cooperation from the patient during the important period of splinting, exercise and massage. If the web between the fingers is loose enough to fan out as the fingers are separated, it is advisable to postpone correction until the child is old enough to cooperate with the dressing, exercises and massage, all of which are necessary to provide a good operative result. The best time is between 6 and 7 years.

The operation he recommends utilizes two V-shaped flaps, one from the dorsum and one from the palmar surface, to line the commissure between the fingers. The denuded areas on the fingers are covered with thick razor grafts from the thighs or with full thickness grafts. He stresses the importance of careful dressing and uniform pressure after the graft has been applied. It has also been found that splinting of these fingers combined with proper physical and occupational therapy must be carried out for a prolonged period in order to produce a satisfactory result.

Arachnodactyly.—Olcott [12] says that arachnodactyly, or Marfan's syndrome, is characterized by elongation and narrowness of the long

12. Olcott, C. T.: Arachnodactyly (Marfan's Syndrome) with Severe Anemia. Am. J. Dis. Child. **60**:660-668 (Sept.) 1940.

bones, particularly those of the metacarpus, the fingers and the toes. It was named *dolichostenomélie* (long narrow limbs) by Marfan in 1896. It is now more generally called arachnodactyly (spider fingers), a term first used by Achard in 1902. Several observers have found a definite familial incidence of arachnodactyly. The condition is important chiefly because of serious lesions that accompany the bony abnormality. As is mentioned by Lloyd and Burch, dislocation of the lenses of the eyes occurs in at least half of the cases. Spinal curvature was reported first by Méry and Babonneix and is usually present, being found especially as kyphoscoliosis. These spinal deformities are generally attributed to muscular weakness rather than to bony deformity.

Olcott reports the case of a girl 15 years and some months old who had arachnodactyly, kyphoscoliosis, congenital cardiac anomalies and cloudiness and displacement of the lenses of the eyes. There were also congenital dislocation of the hip, misplacement of a kidney and atrophy of the frontal lobes of the brain. The patient had severe anemia of the secondary type. Evidence is presented indicating that arachnodactyly and the anomalies associated with it are due to disturbance of the development of the middle germ layer.

Rambar and Denenholz[13] report a case of arachnodactyly with autopsy including histologic examination of the eye. They state: "It is felt that this condition is probably one which occurs in the early embryonic stage, and may be considered an example of defective anlage."

Bean and Fleming[14] give the differential points between arachnodactyly and status dysraphicus, which is like syringomyelia. Patients with the second condition are displayed as the "living skeleton" and the "thin man" at the circus. The authors report a case in which there was an unusual cyst arising from the linings of the sacral canal, a form of spina bifida not heretofore reported, resulting in an equally rare condition causing cephalopelvic disproportion in pregnancy.

Hereditary Edema of the Lower Extremity.—An interesting case of hereditary edema of the legs, or Milroy's disease, has been reported by Rosenberg.[15] This is a rare condition in itself, and in this case it was still more interesting because there were associated congenital anomalies not previously reported. These were: retention of the

13. Rambar, A. C., and Denenholz, E. J.: Arachnodactyly: Report of a Case with Autopsy, Including Histologic Examination of the Eye, J. Pediat. **15**:844-852 (Dec.) 1939.

14. Bean, W. B., and Fleming, J. G.: Arachnodactyly: Report of Case Complicating Pregnancy at Term, Ohio State M. J. **36**:155-160 (Feb.) 1940.

15. Rosenberg, W. A.: Hereditary Edema of Legs (Milroy's Disease) Associated with Other Congenital Anomalies, Arch. Dermat. & Syph. **42**:1113-1121 (Dec.) 1940.

deciduous teeth, the presence of six toes on the left foot, congenital strabismus with amblyopia of the left eye and dystrophy of the hair.

Absence of the Tibia.—Dennison [16] reports a case of apparent congenital absence of the tibia, in which some ossification later took place. A deformed fibula was present. He operated on the knee to impact the fibula between the femoral condyles and was perturbed to find an apparently normal tibial head, articulating in the usual manner with the femoral condyles. Later roentgenograms showed a center of ossification for the tibia. He makes a plea to withhold amputation in cases of this type until a more prolonged investigation is made.

[ED. NOTE: Total absence of a long bone is more rare than partial absence. The literature has taught for some years that a bone is not to be considered totally absent until after the normal time for the appearance of centers of ossification for that bone has elapsed.]

Clubfoot.—Kite [17] in a paper on congenital clubfoot repeats the admonitions given previously, urging physicians who deliver babies with this deformity to send them for treatment early. He states that most clubfooted babies have been delivered by physicians and not midwives, and yet many physicians still do not advise the parents to get early treatment for clubfooted babies. However, progress is being made as a result of the educational campaign for early treatment. The average age of 24 new clubfooted patients treated during 1923 was 31.5 months, while the average age of 25 new patients received in 1938 was only 10 months.

[ED. NOTE: Fifteen years ago one of us (J. H. K.) described in detail a method of correcting clubfoot by casts and wedgings and recommended that in all early cases conservative treatment be used and that forcible manipulation with the patient under an anesthetic and operation be used only for the older patients. He thought that the family physicians could follow these instructions and treat clubfooted babies early. Experience has shown that the family physicians and some of the general surgeons do not have the necessary trained help and equipment to carry on this work successfully; hence he now advises that all clubfooted patients be sent to orthopedic surgeons who specialize in treating this anomaly. He finds that in many cases in which the condition has been only partially corrected by the first treatment correction is more difficult because of the adhesions which follow this treatment and that the time required to correct these relapsed feet

16. Dennison, W. M.: Delayed Ossification of Tibia in Apparent Congenital Absence, Brit. J. Surg. **28**:101-105 (July) 1940.

17. Kite, J. H.: Some Comments on the Treatment of Congenital Clubfeet, J. M. A. Georgia **29**:212-216 (April) 1940.

is longer than for untreated feet. He now advises that treatment be given early and only by an orthopedic surgeon.]

Cozen and Greene [18] report 89 cases of congenital equinovarus in which treatment was by various methods and conclude that improvement of the deformity can be obtained by almost any form of treatment and that the final results are satisfactory but that there is a tendency for the deformity to recur. Shoes were of minor importance in the treatment, and it is felt that in the past too much reliance has been placed in them.

Garceau [19] describes an operation which he found helpful in those cases in which clubfoot recurs after apparently adequate conservative treatment. He thinks that the anterior tibial muscle is the mechanical factor producing the recurrence. He describes an operation in which he frees the attachment of the anterior tibial muscle at its insertion on the medial side of the foot and transplants the tendon into the proximal end of the fifth metatarsal bone. After this the foot is kept in casts for eight weeks, and during this time the ankle is wedged in dorsiflexion until the equinus deformity is well corrected. This operation was performed on 56 feet with no bad effects from the sacrifice of the anterior tibial tendon and with satisfactory end results in 93 per cent of the feet.

[Ed. Note: Probably as long as ten years ago, Dr. John Royal Moore at the Shriners' Hospital for Crippled Children in Philadelphia showed one of us (J. H. K.) patients on whom he had done this same operation. He used it to gain correction in patients being treated for the first time as well as in those in whom there was recurrence. He noted that he had later to replace the anterior tibial tendon in some cases, as it overcorrected the foot. This work was never published.]

Anomaly of the Fifth Toe.—Galland [20] describes the deformity of the fifth toe in which this digit overlaps the adjacent fourth toe. He says that it is due to the presence of an abnormal interdigital web, which tends to produce a recurrence after correction of the deformity. He devised an operation for this condition and says that the skin incision constitutes the basic factor in the operation. The incision is made in the shape of an obtuse angle Z on the dorsum of the foot. Through this incision, all resistant tissue is cut; the operation includes a capsulotomy and a tenotomy. Only the skin is closed, and this falls together in a straight line. The toe is held in slight overcorrection with adhesive tape for six weeks.

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18. Cozen, L., and Greene, W.: Congenital Eqinovarus, West. J. Surg. **48**:697-706 (Nov.) 1940.

19. Garceau, G. J.: Anterior Tibial Tendon Transposition in Recurrent, Congenital Clubfoot, J. Bone & Joint Surg. **22**:932-936 (Oct.) 1940.

20. Galland, W. I.: Operation for Correction of Congenital Overlapping of Fifth Toe, Bull. Hosp. Joint Dis. **1**:93-98 (Oct.) 1940.

II. CONGENITAL DISLOCATION OF THE HIP

Causation.—Storck [21] believes that a hereditary anomalous shape of the uterus may be an endogenous factor in the production of certain congenital deformities, such as dislocation of the hip and torticollis, because it may necessitate deviations in the position of the fetus. As twin pregnancy is a hereditary trait transmissible through the male, he maintains that congenital dislocation of the hip also may be transmitted through the male.

[ED. NOTE: It seems possible that dislocation of the hip in some cases is a secondary deformity due to a restrained position of the fetus within the uterus. Undoubtedly, however, there are numerous cases of primary deformity, due to an extremely early faulty growth of the fetus. In these cases there may be extreme abnormality in the structures of the hip which cannot be explained by mechanical laws, accompanied by other severe deformities, such as arthrogryposis.

Furthermore, in only about 12 per cent of cases has dislocation been proved hereditary. All observations and research are to be welcomed, but certainly at the present time the etiology of congenital dislocation of the hip is obscure.]

Experimental Dislocation of the Hip.—Dislocation of the hip was produced by Whiston [22] in chicks less than 1 day old by prolonged traction without immediate injury to the blood supply of the capsule or the ligamentum teres femoris. They were killed later at intervals up to thirty-two weeks, and careful examination of the dislocated hips was made to determine the pathologic changes attendant on the dislocation.

The ligamentum teres was elongated and thickened by a process of fibrous hyperplasia. [ED. NOTE: In man the ligamentum teres is sometimes broad and thick, sometimes thin, atrophic and weak and sometimes entirely absent.] Cartilage cells were seen mixed with the fibers of the distal third of the ligament, so that there was no sharp demarcation between the ligament and the underlying cartilage of the head.

The vessels in the vascular sheath of the ligamentum teres were either obliterated or greatly reduced in number. This is ascribed to the tension on the vessels and to pressure of the ligament against the margin of the acetabulum. There resulted a degeneration of the blood vessels of the head in the region of the fovea capitis femoris and a mucoid degeneration of the cartilage. In older chicks there was some attempt to repair the degenerative changes.

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21. Storck, H.: Etiology and Early Diagnosis of Congenital Dislocation of the Hip, Med. Klin. **36**:342-343 (March 29) 1940.

22. Whiston, G. C.: Histological Study of Growing Avian Femur (Gallus Domesticus) Following Experimental Dislocation of the Hip, Anat. Rec. **76**:449-521 (April 25) 1940.

Dorsomedial flattening and ovoid distortion of the head together with coxa vara and anteversion of the neck were present. They are ascribed to abnormal tension of the ligamentum teres in the dislocated hip.

Abnormal stresses also produced definite changes in the internal structure, thickening of the cortex on the external convex side of the neck and shaft and thinning on the inner concave side, and thickening of the cortex of the trochanter major. This supports the contention of Koch and others that the internal structure of bone is determined in accordance with mechanical and mathematical laws to produce the greatest strength with a minimum amount of material. [ED. NOTE: This is a careful study of the secondary pathologic changes which occur in a dislocated hip. It does not deal with the primary pathologic conditions and causation of congenital dislocation and consequently cannot explain the entire picture of this lesion.]

Incidence.—Scaglietti [23] reviews and analyzes 15,272 cases of congenital dislocation of the hip. Of the patients, 83.46 per cent were females. In 57.13 per cent of the cases the dislocation was unilateral. Of these cases, the left hip was affected in 65.6 per cent. The condition occurred more frequently in northern than in southern Italy and more often in the plains than in the mountains.

Roentgen Examination and Diagnosis.—Burman and Clark [24] describe minutely the outlines and the markings evident in roentgenograms of infants between 26 days and 12 months of age. They illustrate Perkins' and Shenton's lines together with the lines that may be drawn to box the trochanters and add a line of their own which is drawn tangentially to the short ischiac arm (the iliac border of the Y cartilage of the acetabulum). The value of these lines in determining dislocation of the hip is demonstrated. Roentgen examination of the fetus in utero is shown to have little clinical value. They emphasize the value of diagnosing dislocation of the hip during the early months of life and state that this is fairly easily and accurately done by a proper coordination of clinical signs and roentgen readings. [ED. NOTE: This is a clear detailed exposition of this subject and worth careful study.]

Treatment.—West [25] lays down the following rules for treatment:

1. In children up to the age of 3 years closed reduction should be done and should be followed by immobilization in plaster for nine months.

23. Scaglietti, O.: Modern Trends in the Treatment of Congenital Luxation of the Hip Joint, Chir. d. org. di movimento **25**:308-320 (April) 1940.

24. Burman, M. S., and Clark, H. C.: Roentgenologic Study of Hip Joint of Infant in First Twelve Months of Life, with Reference to Early Diagnosis of Its Congenital Dislocation, Am. J. Roentgenol. **44**:37-47 (July) 1940.

25. West, E. F.: Shelf Operation for Congenital Dislocation of the Hip, M. J. Australia **1**:513-514 (April 13) 1940.

If at the end of this period a roentgen examination shows that the upper lip of the acetabulum is developing satisfactorily, the result will be satisfactory. If not, an operation to form a bony shelf to prevent the upward excursion of the femoral head (acetabulum reconstruction) should be performed at once.

2. If the patients are from 3 to 5 years of age, judgment should be exercised in the selection of treatment. If there is no sign of development of the upper lip of the acetabulum, the operative reconstruction should be done at once. If in a case of unilateral dislocation the acetabulum shows fair development, closed reduction should be tried first. If this is unsuccessful (as measured by the development of the acetabulum) at the end of six months, operative reconstruction should be performed. In a case of bilateral dislocation operation should be done without delay.

3. In children from 5 to 8 years of age, the femur should be pulled down until the head is opposite the acetabulum, or as far down as possible, and then the acetabulum should be reconstructed. Closed reduction is increasingly difficult and is attended with danger of damage to the upper femoral epiphysis and of ankylosis of the hip.

4. After the age of 8 years closed reduction is either impossible or undesirable. If the femoral head is in an anterior position, the function is good, and no treatment is necessary. If it is in a posterior position, West does not favor the construction of a shelf at the site occupied by the head, because this procedure does nothing to correct the lordosis or the length.

He emphasizes the importance of constructing a buttress rather than a shelf above the head of the femur and of turning the roof of the acetabulum downward. He speaks also of the advantages of performing the operation without opening the joint capsule. [ED. NOTE: Most of these rules conform to those enunciated by one of us (A. B. G.), even in his earliest publications.]

Scaglietti [23] reports that at the Rizzoli Institute in Bologna, Italy, in 736 cases the condition was diagnosed during the first year of life and the patient treated by abduction. Excellent results were obtained in 93.92 per cent, which shows the great importance of early diagnosis. The Paci-Lorenz method of reduction was employed in 3,628 cases, with good results in 45 to 50 per cent. Good results were obtained in but 25 per cent after open reduction in 176 cases.

Severin [26] analyzes a study of end results made in 1939 at Vanföreanstalten in Stockholm, Sweden. Of 337 patients (456 hips) treated for congenital dislocation of the hip, only 7 per cent had perfect results. There was subluxation in 15 per cent, redislocation in 15 per cent and

26. Severin, E.: Early Treatment of Congenital Dislocation of Hip, Nord. med. (Hygiea) **5**:59-62 (Jan. 13) 1940.

severe secondary pathologic changes in 51 per cent. He ascribes these bad results to absence of treatment before the second or third year of life and to exaggerated and prolonged immobilization in plaster. He recommends the Waldenström method of fixation after bloodless reduction in a position of 60 degrees of abduction and 90 degrees of flexion, which permits rotation of the femur within the cast. After three or four months the child goes home with crutches, and the hip is kept abducted during the night and in a position of rest during the middle of the day. Physical therapy is employed, and the child begins to walk. Severin recommends Putti's methods of early diagnosis and abduction. [ED. NOTE: Careful studies of end results extending beyond a period of ten years after bloodless reduction have revealed that final results are not nearly as good as was formerly believed. In cases in which the function was considered perfect, even though the acetabulum may not have developed normally, there was later progress to subluxation and loss of function. There is also reason to believe that with some exceptions hips that do not remain reduced after four to six months in plaster will not remain reduced after more prolonged immobilization.]

Unger and Waring [27] maintain that in doing a Schanz osteotomy it is essential to hyperextend as well as to abduct the distal fragment of the femur in order to compensate for lumbar lordosis. They describe a method by which they can measure the amount of hyperextension secured. A flange is attached to the end of each Schanz pin. Before osteotomy the flanges are parallel to each other or lie in the same line, while after hyperextension the lines drawn through the flanges form an angle which is directed forward.

Krinitzky [28] discusses the adverse complications following bloodless reduction by the Lorenz method, particularly in children over 4 years of age. He also states that following the Hoffa-Lorenz method of open reduction there were a mortality of 30 per cent and poor function in patients who survived. For older patients he favors palliative osteotomy. He uses the "shelf" operation for younger children that cannot be cured bloodlessly. He presents a new method of operation to supplant osteotomy. This consists in drilling a large round hole through the femur just below the trochanter major. The drill is so directed that after passing through the femur its tip will impinge on the pelvis just beneath the superior rim of the acetabulum. A large bone transplant that fits the drill hole and has previously been boiled in chemical solu-

27. Unger, H., and Waring, T. L.: Control of Fragments After Osteotomy for Congenital Dislocation of the Hip: Simple Guide for Control of Anterior Angulation, J. Bone & Joint Surg. **22**:448-449 (April) 1940.

28. Krinitzky, J. M.: New Surgical Method in Therapy of Congenital Luxation of Femur, Zentralbl. f. Chir. **67**:1401-1405 (July 27) 1940.

tions is then driven through the hole in the femur so that its inner end passes into the acetabulum just beneath the upper margin. He presents a few cases to demonstrate the efficacy of this procedure. [ED. NOTE: One wonders what may be the eventual fate of this dead graft and what is to be done in advanced stages in which there is little or no acetabular rim persisting.]

Werner [29] cites 2 cases of spontaneous reduction of congenital dislocation of the hip, in which the reduction was proved to be spontaneous by roentgenograms taken before and after the reduction. The patient in the first case was a girl 1½ years of age with a frank dislocation of the left hip and a subluxation of the right. Treatment was advised but not carried out. Two years later all symptoms had disappeared, and the roentgenograms showed the hips were normal. In the second case, a roentgenogram made when the patient was 1 year of age showed a dislocation of one hip, and another made two years later showed a normal hip. No treatment had been given.

III. CONDITIONS INVOLVING GROWING AND ADULT BONE

Pituitary Dwarfism.—One of the functions attributed to the pituitary gland is the control of growth. In cases of pituitary inadequacy, particularly of inadequacy resulting from an infarction of this gland complicating infectious disease, there has been observed a type of dwarfism called the Levi-Lorain type.

Davidoff [30] indicates that the retardation of growth in this disease is likely to be of the infantile type, in which the bones are of light construction and there is generally a childlike build. This is usually associated with a retarded sexual development, but the patients are intellectually normal.

To stimulate growth in pituitary dwarfism Lurie [31] has treated 20 children from 11 to 17 years of age with an extract containing the growth factor of the anterior lobe of the pituitary gland (prepared by Ayerst, McKenna and Harrison) and has obtained a growth in excess of the normal increment expected in children of similar ages.

Schaefer and Strickroot [32] also report their experiences with an anterior pituitary extract containing the growth factor (antuitrin-G) in 18 cases. In 14 of the children there was a definite improvement in

29. Werner, R.: Spontaneous Healing of a Unilateral and a Bilateral Congenital Dislocation of the Hip, Ztschr. f. Orthop. **70**:326-332, 1940.

30. Davidoff, L. M.: Hyperpituitarism and Hypopituitarism, Bull. New York Acad. Med. **16**:227-243 (April) 1940.

31. Lurie, L. A.: Stimulation of Growth in Undersized Children by Means of Endocrine Therapy, J. Med. **21**:205-207 (July) 1940.

32. Schaefer, R. L., and Strickroot, F. L.: Endocrine Dwarfism, Endocrinology **26**:599-604 (April) 1940.

height. It is of interest to note that both of these investigators found it desirable to give these same children thyroid in doses as great as could be tolerated. Although it had been reported in some of these cases that doses of thyroid alone did not stimulate growth, there was demonstrated a synergism that made it desirable to give both glandular preparations to these patients.

The effects of dyspituitarism on the adult skeleton have been studied by Chester and Chester.[33] They made roentgen studies of patients who show the classic characteristics of acromegaly and report their observations on 8 patients. Five of these showed low dorsal kyphosis. The vertebrae of these patients showed an increase in the size of the bodies characterized by an accretion of bone on the anterior and lateral aspects. The height of the vertebral bodies remained the same. The disks, too, showed enlargement in the same directions as the bodies. This came about by abnormal growth of the perichondrium. At times the compression of the disks produced narrowing of the intervertebral space. These changes were more noticeable in the lower thoracic than in the lumbar portion of the spine. Osseous rims could frequently be found, but these rims differed from arthritic spurs in that the pituitary ridges were usually symmetric while the overgrowths attributable to arthritis were irregular spiculations.

The Thyroid Gland and the Skeletal System.—The effects of hypothyroidism have been observed in cretins and have been subjected to careful study. By means of the administration of thyroid it has been possible to learn the role played by the thyroid gland on the skeletal system. Wilkins[34] has compared the rate of osseous development and of mental development of patients with hypothyroidism with that of normal children. He states that by administering subtoxic doses of desiccated thyroid he is able to produce a growth curve that parallels, and at times is better than, that of the normal growth curve.

Kerley[35] reports the cases of 2 patients with congenital myxedema who under subtoxic thyroid therapy have grown up with normal physical and intellectual qualities.

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33. Chester, W., and Chester, E. M.: Vertebral Column in Acromegaly, Am. J. Roentgenol. **44**:552-557 (Oct.) 1940.

34. Wilkins, L.: The Rates of Growth, Osseous Development, and Mental Development in Cretins as a Guide to Thyroid Treatment, J. Pediat. **12**:429-438 (April) 1938; The Pharmacopeia and the Physician: Thyroid Medication During Childhood, J. A. M. A. **114**:2382-2387 (June 15) 1940; Recent Studies on the Diagnosis of Hypothyroidism in Children, Pennsylvania M. J. **44**:429-432 (Jan.) 1941.

35. Kerley, C. G.: End Results in the Cretin, Arch. Pediat. **57**:432-436 (July) 1940.

The studies of Wilkins [36] are of particular interest in their clarification of epiphysial changes that have hitherto not been generally understood. There is present in patients with hypothyroidism an abnormality of the centers of ossification that simulates the changes of Legg-Perthes disease. These conditions are, however, distinct entities. Ossification of the normal epiphysis develops from a single focus in the center of the epiphysial cartilage. In hypothyroidism, however, there are multiple irregular foci scattered through the epiphysial plate. As these enlarge and coalesce there is presented a roentgen picture of stippling or fragmentation. This condition, named by Wilkins epiphysial dysgenesis, responds favorably to thyroid therapy. Epiphyses that have been retarded in their ossification because of the hypothyroid condition may show the dysgenetic changes even after therapy has been started, but ultimately the coalescence of the multiple centers leads to a normal-looking epiphysial calcification.

There is, however, a type of stippling that is not attributable to thyroid dysfunction. This condition, the epiphysial dysplasia punctic-ularis, is apparently a distinct entity of unknown origin.[37]

Parathyroid Glands and Bony Changes.—The relation that exists between the parathyroid glands and changes in bone has been well established. The recent literature [38] contains many reports that bear out the present concepts. Coordination of the various manifestations of hyperparathyroidism is accomplished by Kyser,[39] Bowers [40] and Rynearson.[41]

An excellent study is presented by Jaffe.[42] In addition to a presentation of the theoretic concepts and the clinical picture he makes

36. Wilkins, L.: Epiphyseal Dysgenesis Associated with Hypothyroidism, Am. J. Dis. Child. **61**:13-34 (Jan.) 1941.

37. McCullough, J. A. L., and Sutherland, C. G.: Epiphysial Dysplasia Punctic-ularis (Stippled Epiphyses): Report of Case Not Associated with Hypothyroidism, Radiology **34**:131-135 (Feb.) 1940.

38. Hart, D., and Gardner, C. E., Jr.: Hyperparathyroidism: Report of Nine Cases, South. Surgeon **9**:41-58 (Jan.) 1940. Baumgartner, C. J.: Hyperparathyroidism—Normal Chemistry—Rapid Recalcification Following Removal of Large Parathyroid Adenoma, West. J. Surg. **48**:324-327 (May) 1940. Heller, E. P.: Hyperparathyroid Disease and Manifestations of Interest to Industry, Indust. Med. **9**:125-135 (March) 1940.

39. Kyser, F. A.: Hyperparathyroidism, Proc. Staff Meet., Mayo Clin. **15**: 179-181 (March 20) 1940.

40. Bowers, R. F.: Hyperparathyroidism, Internat. Clin. **3**:277-285 (Sept.) 1940.

41. Rynearson, E. H.: Hyperparathyroidism, M. Clin. North America **24**:1027-1033 (July) 1940.

42. Jaffe, H. L.: Hyperparathyroidism, Bull. New York Acad. Med. **16**:291-311 (May) 1940.

a careful survey of the pathologic changes in the skeleton. He indicates that the bony changes observed, even in patients with moderate bony porosity, are characterized by the perforation of the bony trabeculae by connective tissue tracts. Osteoclastic action is noted with little evidence of new bone formation. Instead, the connective tissue forms islands in the decalcified areas, and as the disease progresses there is an enlargement of these islands so that the connective tissue masses ultimately merge to make large fibrous scars. Though these fibrous scars are distributed generally, they are likely to be present with greater frequency in the bones that are subjected to the largest amount of functional stress, such as the long tubular bones, the vertebral column and the terminal phalanges of the fingers (clubbed fingers). He explains the development of the brown tumor on the basis of formation of such a decalcified area with subsequent cystic degeneration produced by ischemia or hemorrhage. He emphasizes the importance of not confusing the solitary giant cell tumor with the brown tumor and takes up in detail the differential diagnosis of this condition as well as of other confusing diseases.

A rather interesting study is reported by Helfet.[43] Working on the theory that parathyroid dysfunction produces changes in the phosphorus rather than in the calcium of the skeleton, he has been prescribing aluminum acetate in the belief that the aluminum will combine with the phosphate in the intestine to form aluminum phosphate. This product is then excreted by the bowel. He offers several case reports to show that under such therapy the patients improved. The astringency of the drug has made it necessary to administer the medication in small doses, but he has found slow but definite improvement in the condition of his patients. He also links rheumatoid arthritis with hyperparathyroidism and therefore administers aluminum acetate to rheumatic persons. In these patients, too, he has found a definite improvement. [ED. NOTE: The evidence against this "new conception" is so strong that more adequate substantiation of the author's thesis is desirable.]

At this point attention should also be called to polyostotic fibrous dysplasia, a condition which is often mistaken for a manifestation of hyperparathyroidism or for the so-called solitary bone cyst. Although the patient of Moehlig and Schreiber [44] showed abnormalities that were attributable to dyspituitarism, they felt convinced that the bony changes

43. Helfet, A. J.: New Conception of Parathyroid Function and Its Clinical Application: Preliminary Report on Results of Treatment of Generalized Fibrocystic and Allied Bone Diseases and of Rheumatoid Arthritis by Aluminum Acetate, Brit. J. Surg. **27**:651-677 (April) 1940.

44. Moehlig, R. C., and Schreiber, F.: Polyostotic Fibrous Dysplasia: Report of Case with Unilateral Involvement, Am. J. Roentgenol. **44**:17-23 (July) 1940.

represented a skeletal developmental anomaly. Adams and associates [45] report 10 similar cases and found that these changes appear early in childhood after monomelic tendencies and are usually called to the attention of the physician because of pain, fractures and malunion. Since the causation of this condition is not clear and since the cystic changes cannot be eradicated by operation, they recommend limiting treatment to procedures giving symptomatic relief and preserving normal function.

Growth Deficiency from Hypogonadism.—Growth deficiencies can also result from hypogonadism. Under treatment with testosterone propionate [46] a 15½ year old eunuch showed a spurt in growth that brought him to a much more normal height. The ratio of the length of the long bones to the length of the short bones likewise became far more normal than before treatment. Chorionic gonadotropin [47] administered for sexual underdevelopment was also found to be an excellent stimulant to bone growth. Observations on the effects of such treatment on 21 patients with genital dystrophy showed considerable improvement in the rate of skeletal development. The value of treatment with chorionic gonadotropin is most apparent in children under 13 years of age, while its administration to children under 5 years requires great caution. In general, it was noted that the taller boys have relatively moderate rises in the growth curve, while the more stunted patients have much more marked spurts in growth. There is also a concomitant acceleration in osseous development of the carpal bones as indicated by roentgenograms. There is, on the other hand, no evidence of premature closure of the epiphyses. It is possible that the increase in height may be produced by the stimulation of the gonads, which in turn stimulate the growth factor in the anterior pituitary lobe. In one report [48] it is suggested that hypogonadal skeletal changes are characterized by thinning of the cortical layer and of the bony trabeculae, by roughening of the metaphysial margin of the growing bone and by an associated tendency to dental caries.

Brittle Bones.—The possibility that bone fragility of the type associated with blue scleras, usually attributed to a hereditary mesenchymal

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45. Adams, C. O.; Compere, E. L., and Jerome, J.: Regional Fibrocystic Disease, Surg., Gynec. & Obst. **71**:22-32 (July) 1940.

46. Rapfogel, I.: Effect of Testosterone Propionate upon Skeletal Development of a Eunuch, Endocrinology **27**:179-184 (Aug.) 1940.

47. Dorff, G. B.: Chorionic Gonadotropic Effects on Height and Osseous Development in Sexually Underdeveloped Young Boys, Endocrinology **27**:403-410 (Sept.) 1940; Chorionic Gonadotropic Effects on Growth of Sexually Underdeveloped Older Boys, Am. J. Dis. Child. **60**:1043-1057 (Nov.) 1940.

48. Hurxthal, L. M., and Hare, H. F.: Bone Changes in Primary Hypogonadism, Lahey Clin. Bull. **1**:9-12 (April) 1940.

hypoplasia, is etiologically related to Paget's disease is suggested by the case of Nichols.[49] The presence of otosclerosis as part of the syndrome is indicated by Fox and Sweet,[50] in whose cases there is evidence that development of deafness takes place in patients who pass their twentieth birthday.

In this connection it is interesting to note Funk's[51] opinion that there has been confusion in the literature about fragilitas ossium. He differentiates Lobstein's osteopsathyrosis from Vrolik's osteogenesis imperfecta. The latter is characterized by deformities of growth, occurrence of fractures in utero and early death, usually before the child becomes 4 years old. The blue scleras constitute, in his opinion, an unreliable sign. In the Lobstein type, there are no disturbances of growth. The fractures usually begin after 2 years of age, and the patient may live a normal span of life. Although he considers the condition a hereditary constitutional anomaly, he questions the relation to parathyroid malfunction and points out that treatment with thymus extract, estrogens, androgens and adrenal, thyroid and pituitary extracts has failed to give relief. In his own case, a diet high in calcium and phosphorus with vitamin D failed to produce improvement.

Osteopetrosis.—The peculiar osteodystrophic disease, osteopetrosis, described by Albers-Schönberg has received some attention. Its existence without the production of any symptoms is emphasized by Howard and Gonzalez,[52] who accidentally found marble bones in a young woman who was being given a roentgen examination for a possible foreign body. In another case report[53] autopsy studies of a 1 year old baby indicated that compensatory myeloid changes may occur in the lymph nodes, spleen and liver. In this patient, too, periosteal reaction was observed in conjunction with the sclerotic changes in the bones. The production of generalized osteosclerosis by an exogenous factor is called to one's attention by several observers. Wilkie[54] reports 2 cases of

49. Nichols, B. H.: Fragilitas Ossium: Brittle Bones and Blue Sclerae; Hereditary Mesenchyme Hypoplasia, Cleveland Clin. Quart. **7**:58-65 (Jan.) 1940.

50. Fox, M. S., and Sweet, S. J.: Brittle Bones Associated with Deafness and Blue Scleras: Report of Syndrome in Two Persons of One Family, Arch. Otolaryng. **32**:506-511 (Sept.) 1940.

51. Funk, P.: Lobstein's Osteopsathyrosis: Syndrome of Abnormal Fragility of Bones with Blue Sclera and Tympanic Membrane, Schweiz. med. Wchnschr. **70**:473-479 (June 1) 1940.

52. Howard, C., and Gonzalez, J.: Osteopetrosis: Report of a Case, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **3**:165-171 (Oct.) 1940.

53. Beatty, S. R., and Ritchie, G.: Osteopetrosis: Case Report, Radiology **34**:338-342 (March) 1940.

54. Wilkie, J.: Two Cases of Fluorine Osteosclerosis, Brit. J. Radiol. **13**:213-217 (June) 1940.

osteosclerosis caused by exposure to fluorine compounds. Two other communications indicate that osteosclerosis can be produced by drinking water that contains an excessive amount of fluorine. Apparently these patients usually show mottled tooth enamel and hardening of the bones that may vary in degree from thickening of the vertebrae to complete osteopetrosis. In Madras, India, where the disease was endemic on account of the high fluorine content of the water, the disease was frequently ushered in by rheumatic pains, chiefly in the back, shoulders and hips, and often showed pathologic changes in the ligaments, which lost their elasticity and became ossified. The differences shown by the various groups of cases reported lead one to believe that osteopetrosis is a manifestation of several conditions which may be etiologically and pathologically independent.

Osteoporosis.—Senile osteoporosis is no longer being dismissed with the comment that "it is the bone atrophy of old age." Black [55] studied 208 cases of vertebral osteoporosis. He found that women are much more subject to this condition than men, a ratio of 4 to 1. His patients were all over 45, averaging 62 years of age. The clinical pictures presented varied considerably. Some patients had no symptoms referable to this. Others, however, had aching in the lower part of the back with weakness and fatigue. This discomfort could be precipitated by light strain into an acute backache with sharp radiations of pain. Most of the patients showed a flattening of the normal lumbar curve with a marked increase in the thoracic kyphosis and an exaggerated cervical lordosis. Occasionally movements were found to be considerably restricted. Roentgen examinations showed pronounced atrophy of the vertebrae, with development of biconcave bodies and expanded intervertebral disks. In the treatment, dietary supervision was undertaken to assure the proper ratio of carbohydrate, fats, proteins and vitamins, with additional large amounts of calcium and phosphorus. No definite improvement could be attributed to diet alone. Relief, however, could be obtained by supporting the back and applying local physical therapy.

An interesting chemical analysis of bone in a 10 year old child is presented by Hansen, Palmer and Nelson.[56] This child had extensive carcinoma of the liver and showed thinning of the bones early in the disease. A specimen of bone showed a marked replacement of bone

55. Black, J. R.: Senile Osteoporosis of Spine, Proc. Staff Meet., Mayo Clin. **15**:619-623 (Sept. 25) 1940.

56. Hansen, A. E.; Palmer, L. S., and Nelson, J. W.: Composition of Bone in Extreme Osteoporosis Associated with Hepatoma, Proc. Soc. Exper. Biol. & Med. **43**:206-207 (Jan.) 1940.

by water and lipids and about one third less than normal of calcium, phosphorus, magnesium and carbon dioxide.

Brown and Ginsburg [57] present the case of a patient with bone atrophy and metastatic calcification associated with severe glomerulonephritis. They feel that the skeletal demineralization may have resulted from prolonged acidosis with increased thyroid activity.

Chondroplasias.—Judging from the large number of reports on epiphysial dysplasias, there is a growing interest in such diseases as achondroplasia and dyschondroplasia (Ollier's disease). Archeologically,[58] achondroplasia has been traced practically to the neolithic era. In Egypt, a humerus showing signs of this anomaly was found in the tomb of King Zer of the First Dynasty; a complete achondroplastic skeleton has been found that has been assigned to the predynastic period, the Badarian era. Therefore, this is one of the oldest diseases known.

Usually achondroplasia does not become apparent until years after birth. Thalheimer and Gershon-Cohen,[59] however, indicate that it is possible to diagnose such a condition prenatally. They refer to Cronberg, who reported a case of achondroplasia recognized before birth by means of roentgen examination. In their own case the condition was not diagnosed till six months after delivery, but by referring to the prenatal roentgenograms they were able to see changes that could have warranted the diagnosis before birth. The changes observed were lumbar kyphosis, irregularity of the lumbar vertebral bodies, widened and deformed costochondral junctions and short and wide bony shafts that were flared at the ends.

Diagnosis of the chondroplasias in growing children and in adults is not without difficulties. Partly this may be attributed to the profusion of names for the manifestations, names used interchangeably by some authors.[60] The differential diagnosis is made difficult by the similarity of the specimens to those of cartilaginous tumors. Carter [61] reports a case in which roentgenograms, photographs and specimens suggest a neoplasm, but both he and Phemister classify the case as one of Ollier's

57. Brown, C. L., and Ginsburg, I. W.: Osteoporosis Associated with Extensive Metastatic Calcification and Chronic Renal Disease, Arch. Path. **30**:108-121 (July) 1940.

58. Bleyer, A.: Antiquity of Achondroplasia, Ann. M. Hist. **2**:306-307 (July) 1940.

59. Thalheimer, E. J., and Gershon-Cohen, J.: Chondrodystrophy: Prenatal Diagnosis Possible, Radiology **35**:495-496 (Oct.) 1940.

60. Zimmermann, C. A. W.: Hereditary Deforming Chondrodysplasia, J. Missouri M. A. **37**:294-298 (July) 1940.

61. Carter, R. M.; Ollier's Dyschondroplasia: Report of Case, J. Bone & Joint Surg. **22**:1063-1069 (Oct.) 1940.

dyschondroplasia. The condition is further complicated by the possibility of neoplastic changes in a true hereditary or congenital deformity. Gillespie and Siegling [62] call attention to the confusion of Morquio's disease (osteochondrodystrophia deformans) with dysostosis multiplex. The latter disease is characterized by dwarfed stature, scaphocephalic and chondrodystrophic deformities of the skull, shortness of the neck and trunk, abdominal protrusion, kyphosis of the spine, partial ankylosis of the joints and clouding of the cornea. It is emphasized that though Morquio's disease is familial and usually associated with normal mentality, dysostosis multiplex is congenital, shows a retarded mentality and usually is accompanied by the nonskeletal symptom clouding of the cornea. The hereditary character of the disease is stressed by Mörch.[63] Jacobson [64] explains the structure of epiphysis-like exostoses on the basis of a mutual polarity that exists wherever cartilage and bone are growing together. Butler and Debenham [65] demonstrate that secondary disease can result from the bony masses; they report a case in which there was a false saccular aneurysm produced by pressure and erosion on the femoral artery. Abell [66] reports a patient with 91 tumors.

Paget's Disease.—The writings on osteitis deformans consist chiefly of reports of cases. Though there has been no great progress in the understanding of the causes or treatment of this disease, it becomes clear that the condition is not rare. Sugarbaker [67] reports 51 cases from the Henry Ford Hospital. The patients were all above 40 years of age. The bones most frequently involved were the skull, the spine, the pelvis, the femur and the tibia. Involvement of a single bone was present in 24 per cent of the patients. The pain of these patients could be attributed to the tension on the periosteum and ligaments. The chemical studies revealed normal blood calcium and phosphorus, but the phosphatase readings showed an increase that varied with the extent of osseous involvement (average, 12.74 Bodansky units). Fractures may complicate the course of the disease (15 per cent), and sar-

62. Gillespie, J. B., and Siegling, J. A.: Dysostosis Multiplex, J. Bone & Joint Surg. **22**:171-175 (Jan.) 1940.

63. Mörch, E. T.: Achondroplasia Is Always Hereditary and Is Inherited Dominantly, J. Hered. **31**:439-444 (Oct.) 1940.

64. Jacobson, S. A.: Contribution to Pathogenesis of Multiple Hereditary Osteochondromatosis: Experimental Study, Am. J. Cancer **39**:220-223 (June) 1940.

65. Butler, E., and Debenham, M. W.: Traumatic False Saccular Aneurysm Resulting from Erosion of Femoral Artery in Patient with Hereditary Deforming Chondrodysplasia, West. J. Surg. **48**:511-513 (Aug.) 1940.

66. Abell, I.: Chondrodysplasia—Report of a Case, Arch. Surg. **41**:213-220 (Aug.) 1940.

67. Sugarbaker, E. D.: Osteitis Deformans (Paget's Disease of Bones): Review of Fifty-One Cases, Am. J. Surg. **48**:414-421 (May) 1940.

comatous degeneration occurs sufficiently often to make one be on the alert for the condition, especially after the disease has been present for ten or fifteen years.

Attempts to attribute this disease to disturbances of the endocrine system have not been convincing. Rose [68] reports 3 cases, in 2 of which there was concomitant diabetes mellitus. Nichols [69] calls attention to the resemblance of the bony changes in Paget's disease to those in hyperparathyroidism but stresses that each of these diseases has definite diagnostic features and that they should not be confused. The possibility of mistaking the headache of Paget's disease for that of pituitary neoplasm is presented by Pond,[70] and differential diagnosis of the two is given. The therapy for osteitis deformans is still unsatisfactory, though there have been encouraging results reported from the use of extracts of adrenal cortex.

Xanthomatosis.—Hertzog, Anderson and Beebe [71] performed an autopsy on a patient who had died from a fatal aplastic anemia and observed changes in the fat storage which suggested Hand-Schüller-Christian disease. Although there were no gross bony changes to be found clinically, the bone marrow in the shaft of the femur was red and hypoplastic on microscopic examination. Jelsma [72] reported 3 cases with typical cranial defects in which roentgen therapy produced a 60 per cent improvement.

Rickets.—Assuming that rickets develop in the premature infant unless adequate preventive measures are taken, Zelson [73] studied the effects of single massive doses of vitamin D in 46 premature infants. In most of his cases 600,000 U. S. P. units in the form of vitamin D_2 (calciferol) or D_3 (activated 7-dehydrocholesterol) was administered parenterally. Rickets did not develop in any of the patients so treated.

Vollmer [74] discusses the question of the toxicity of large doses of vitamin D. He indicates that in the irradiated ergosterols there are present many by-products which may prove toxic. If, however, one can

68. Rose, M. E.: Paget's Disease, Illinois M. J. **77**:232-234 (March) 1940.

69. Nichols, D. R.: Osteitis Deformans (Paget's Disease of Bone): Report of Case, Proc. Staff Meet., Mayo Clin. **15**:182-184 (March 20) 1940.

70. Pond, C. W.: Paget's Disease, Pituitary Tumor and Abscess of Sphenoid Sinus: Report of Case, Ann. Otol., Rhin. & Laryng. **49**:500-509 (June) 1940.

71. Hertzog, A. J.; Anderson, F. G., and Beebe, G. W.: Reticulo-Endotheliosis with Lipoid Storage, Arch. Path. **29**:120-124 (Jan.) 1940.

72. Jelsma, F.: Xanthomatosis: Report of Three Cases, South. M. J. **33**: 1256-1260 (Dec.) 1940.

73. Zelson, C.: Prevention of Rickets in Premature Infants with Parenteral Administration of Single Massive Doses of Vitamin D, J. Pediat. **17**:73-78 (July) 1940.

74. Vollmer: Treatment of Rickets and Tetany by Parenteral Administration of One Massive Dose of Vitamin D, J. Pediat. **16**:419-432 (April) 1940.

administer calciferol or activated 7-dehydrocholesterol alone, the toxic dose is many times greater than the one necessary for treatment. On the basis of results obtained in 158 children he advocates the use of a single massive dose, usually 600,000 U. S. P. units of vitamin D. No toxic manifestation appeared in any of the children so treated.

The method of giving vitamin D preparations also comes up for discussion. Vollmer prefers the parenteral route. Because administration of the usual oily solution is an uncomfortable procedure and because there is an appreciable delay in the utilization of the vitamin so administered, he suggests adding ether to the oily mixture. This technic has resulted in much more rapid utilization of the effective agent; according to his experience the serum calcium and phosphorus can become normal within three to seven days and calcification can be shown roentgenographically within a week. Complete recalcification was usually found at the end of a month.

Albright and others [75] report an interesting case of rickets associated with dwarfism and nephrocalcinosis. The patient, a girl 13 years old, showed normal serum calcium and low serum phosphorus and high serum phosphatase, clearly demonstrating the rachitic nature of her disease. She had massive calcareous deposits in the kidneys, hyperchloremia and a low level of serum carbonates. In addition to this, she showed a marked retardation in growth. The authors interpret the clinical picture in the following way: There was an inability to produce ammonia together with a failure to excrete acid urine as a result of renal disease. Furthermore, there was an inadequate amount of base with which to excrete the mineral acid. The calcium substituted for the base and was lost through urinary excretion, producing a low level of serum calcium. This stimulated secondary parathyroidism, with resultant hypophosphatemia and low phosphorus rickets. When the patient was given a low sodium chloride diet reenforced with vitamin D and sodium citrate and citric acid, there was definite improvement in her condition. Albright does not consider this a case of renal rickets but prefers to call it one of nephrocalcinosis with rickets and dwarfism.

Scurvy.—There have been many clinical reports of patients suffering from scurvy as a result of dietary deficiencies. There has also been a considerable amount of experimental work on animals in which scurvy was produced. Crandon, Lund and Dill,[76] however, have experimentally produced scurvy in an adult human being and have carefully studied the manifestations. A man was placed on a vitamin C-free diet

75. Albright, F., and others: Metabolic Studies and Therapy in Case of Nephro-Calcinosis with Rickets and Dwarfism, Bull. Johns Hopkins Hosp. **66**:7-33 (Jan.) 1940.

76. Crandon, J. H.; Lund, C. C., and Dill, D. B.: Experimental Human Scurvy, New England J. Med. **223**:353-369 (Sept. 5) 1940.

that was kept supplemented with all other known vitamins. This regimen was maintained for a period of six months. The earliest clinical manifestations did not appear until one hundred and thirty-two days of adherence to this diet had elapsed. The tests for scurvy generally used did not prove to be sensitive indexes in the early stages of the disease. Thus, the plasma ascorbic acid level was zero for thirteen weeks before the first evidence of clinical disease was noted. The vitamin level in the white cell–platelet layer of the centrifuged blood, however, proved to be a good index of the patient's status with regard to vitamin C. The first definite clinical sign consisted of hyperkeratotic papules containing ingrowing hairs. Failure of wound healing was an important finding, the tissues showing a lack of intercellular substance. There was no evidence of lowered resistance to infection in the scorbutic state. The scurvy responded rapidly to intravenous injection of ascorbic acid.

Caisson Disease.—Caisson disease is caused by too rapid decompression after tissues have become saturated with nitrogen gas. During compression the pulmonary air is saturated with nitrogen under pressure. The nitrogen is carried to the tissues, whereupon the entire body becomes saturated. Fat takes up five times more nitrogen than other tissues. Complete saturation with nitrogen requires about one hour, but this time is shortened by exercise. During the decompression the reverse process takes place. The saturated tissues give off nitrogen to the blood, which becomes desaturated in the lungs until atmospheric pressure is reached. If decompression is too rapid, bubbles of nitrogen form in the body and cause embolism. Emboli so formed are most common in venous blood, fatty tissues, synovial fluid and structures of the nervous system.

Coley and Moore [77] tabulate systematically the symptoms of caisson disease as follows: (1) cerebrospinal—numbness, tingling, coma, collapse, Ménière's syndrome; (2) cardiovascular—signs of embolism; (3) pulmonary—dyspnea; (4) visceral—nausea and vomiting; (5) dermal—pruritus; (6) skeletal—pain present in 85 to 90 per cent of cases.

The long bones are the favored sites; the vertebrae and the membranous bones escape, perhaps because of the high proportion of red marrow as compared with fatty marrow. The lower extremities are affected more often than the upper. The pain is due to gas being confined in an unyielding space.

The pathologic change which accompanies caisson disease is caused by nutritional disturbance as a result of embolism or pressure on a blood vessel from without or both. The result is aseptic necrosis which

77. Coley, B. L., and Moore, M., Jr.: Caisson Disease with Special Reference to Bones and Joints: Report of Two Cases, Ann. Surg. **111**:1065-1075 (June) 1940.

is followed by attempts at repair by osteoclasis, creeping substitution and eventual delimitation by calcification.

The lesions are distinguished roentgenographically by their multiple distribution in medullary bone. The osseous shaft is not expanded, and the infarction presents a region of irregularly increased density surrounded by a region of calcification on the outside of which is normal bone. According to Walker,[78] this region is necrotic bone with empty lacunar spaces walled off by a thin rim of calcium. The articular changes resemble roentgenographically those of arthritis deformans.

Rendich and Harrington [79] sum up the chronic osseous changes of caisson disease as follows: (1) aseptic necrosis of hips, shoulders or knees; (2) medullary calcification in diaphysial ends of long bones; (3) hypertrophic arthritis, (4) aseptic necrosis with osteoarthritis as well as medullary calcification.

Coley and Moore [77] express the belief that the characteristic lesions of the bones can result from one insult of sufficient severity and that caisson disease may be the cause of vague pains in the bones and joints caused by regions of aseptic necrosis which may later be discovered. They stress the importance of the clinical picture in the field of compensation claims.

Gordon and Heacock [80] present a case in which the presence of air in the synovial space was demonstrated roentgenographically. To their knowledge this is the first case on record in which the clinical diagnosis was supported roentgenographically.

IV. TUBERCULOSIS OF BONES AND JOINTS

General Considerations.—Meyer and Froyez-Roederer [81] report their studies at the Franco-American Foundation of Berck-Plage to determine the frequency of infection by the bovine tubercle bacillus. Pus obtained by puncture or more rarely from fistulas in 239 cases of osteoarticular tuberculosis and in 23 cases of tuberculosis of the cervical lymph nodes was studied by culture and, when necessary, by animal inoculation. Of the 250 strains of tubercle bacilli isolated, 242 were the human type and 8 the bovine type. There were 5 bovine infections in 235 cases of osteoarticular tuberculosis and 3 bovine infections in 12 cases of tuberculosis of the cervical lymph nodes.

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78. Walker, W. A.: Aseptic Necrosis of Bone Occurring in Caisson Disease: Case Report, J. Bone & Joint Surg. **22**:1080-1084 (Oct.) 1940.

79. Rendich, R. A., and Harrington, L. A.: Roentgen Findings in Caisson Disease of Bone, with Case Reports, Radiology **35**:439-448 (Oct.) 1940.

80. Gordon, J. O., and Heacock, C. H.: Roentgenologic Demonstration of Localized Gas in Caisson Disease, J. A. M. A. **114**:570-571 (Feb. 17) 1940.

81. Meyer, K., and Froyez-Roederer: The Frequency of Infection with Bovine Bacilli in Osteo-Articular and Cervical Lymph Node Tuberculosis, Ann. Inst. Pasteur **64**:167-172 (Feb.) 1940.

Combining their observations with those of other investigators in France, they obtained 7 cases of bovine bacillus infection in 445 cases of tuberculosis of the cervical lymph nodes. They conclude that the bovine tubercle bacillus plays an unimportant part in causing the disease in France. This is considered due to the infrequent consumption of raw milk.

In postulating the role of the pleural lymphatics in the pathogenesis of cold abscesses of the wall of the chest and paravertebral abscesses, Burke [82] says that particulate matter (a mixture of colloidal thorium dioxide and finely divided lampblack and tubercle bacilli in suspension in isotonic solution of sodium chloride) injected into the pleural spaces of guinea pigs is, in part at least, transported to the parasternal and the para-aortic lymph nodes. Observations on human subjects who have come to necropsy indicate that in man tubercle bacilli and particulate matter, such as silicious material, are conveyed from the pleural spaces to the parasternal and para-aortic lymph nodes. This evidence provides a probable explanation of the formation of cold abscesses of the anterior wall of the chest, and makes it seem probable that the transfer of tubercle bacilli from the pleural spaces to the para-aortic lymph nodes may in certain instances play a part in the evolution of paravertebral abscesses. [ED. NOTE: In our experience paravertebral abscesses and abscesses of the anterior wall of the chest unassociated with foci in the vertebrae, the ribs or the sternum are rare.]

Law [83] gives the history of a case which he states was one of multiple cystic tuberculosis of bones. The patient was a 6 year old girl with tuberculosis of the dorsal portion of the spine and pulmonary tuberculosis. While she was under treatment for this condition by spinal fusion and rest, multiple cystic lesions of the Jüngling type and entirely asymptomatic were found involving 22 bones; none of the lesions were in the small bones of the hands and feet. Serial roentgenograms were taken of all lesions. Healing of every lesion was shown to take place spontaneously, anywhere from five and a half to forty-eight months after the patient came under observation. The roentgen observations of diagnostic value are discussed. These include round, smooth or irregular punched-out areas of decreased density, with a thin cortex and little or no surrounding sclerosis and without periosteal involvement, expansion or abscess formation.

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82. Burke, H. E.: Role of Pleural Lymphatics in Pathogenesis of Cold Abscesses of Chest Wall and Paravertebral Abscesses, J. Thoracic Surg. **9**:506-519 (June) 1940.

83. Law, J. L.: Multiple Cystic Tuberculosis of Bones: Its Roentgen Picture and Reparative Process as Seen in Serial Roentgenograms, Radiology **35**:328-335 (Sept.) 1940.

Ellis [84] calls attention to the evidence that Jüngling's disease is osteal sarcoid and not cystic tuberculosis of the bones, as it is considered by many American authors. Cases of this disease have the following characteristics: There is lack of necrosis in the lesions; sinuses do not form; usually the patient does not react to old tuberculin; the lesions are solid and appear to be cystic only in the roentgenogram.

Because of the rarity of tuberculosis of shafts of the long bones in the United States, as revealed by an intensive search of the literature, Carrell and Childress [85] sent a questionnaire to 250 leading orthopedic surgeons in the United States and collected a series of 95 cases.

In every case in this group the condition had been definitely proved to be tuberculous by microscopic section and animal inoculation, or by the latter method alone. Only lesions of shafts (diaphyses and metaphyses without involvement of the joints) of long bones were accepted. Whether a lesion was in the diaphysis or the metaphysis is not recorded. In 95 patients, 123 long bones of the extremities were affected. Seven patients had involvement of 2 bones; 4, of 3 bones; 2, of 4 bones; and 1, of 7 bones. The tibia was involved in 36 patients (29 per cent), and the femur was affected in 33 (27 per cent). This marked frequency of occurrence in these 2 bones was present uniformly, regardless of the age group.

Contrary to current opinion, shaft tuberculosis does not occur predominantly in childhood. Of this series of 95 patients, 46 (48 per cent) were 20 years of age or more at the time of onset. Associated active tuberculous lesions were present in 37 patients. Of the total series of 95 patients, only 11 had involvement of the joints.

Eighteen deaths occurred in 95 patients. Seventeen of these deaths were in patients with allied lesions, and 14 deaths were in patients with a duration of symptoms of one year or less.

The end results were known in 71 of the 95 cases. Healing occurred in 92 per cent of 13 patients treated by curettage or saucerization and closure. In 3 cases bone chips were packed into the osseous cavity after curettage. The addition of chips may aid in a more rapid repair of the defect. Of the 38 cases in which treatment was by incision and drainage, healing took place in 25 (66 per cent); there was no improvement in 6, and death occurred in 7. In many of these cases, in which there were draining sinuses, conditions were not suitable for closure, and in others, no doubt, there had first been surgical treatment after a diagnosis of pyogenic osteomyelitis.

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84. Ellis, F. A.: Jüngling's "Osteitis Tuberculosa Multiplex Cystoides" Is Not Cystic Tuberculous Osteitis, Acta med. Scandinav. **104**:221-224, 1940.

85. Carrell, W. B., and Childress, H. M.: Tuberculosis of Large Long Bones of Extremities, J. Bone & Joint Surg. **22**:569-588 (July) 1940.

There were only 5 instances of spontaneous healing. The facts that 37 patients had had symptoms for over one year and that 19 had had complaints for over two years before being treated demonstrate the fallacy of the inference that healing might eventually have taken place in more patients if surgical intervention had been delayed.

[ED. NOTE: Tuberculosis of diaphyses of long bones is rare, but lesions of metaphyses without involvement of the joints are more common. Although the number of patients so treated is not large, it would appear that curettage or excision of the lesion and closure of the wound give the best results.]

Operative Treatment of Tuberculosis of Bones and Joints.—Bosworth [86] writes of various aspects of the treatment of tuberculosis of bones and joints. This is based on experience with a large number of cases in a New York municipal hospital devoted to the care of tuberculous patients. He stresses the importance of the patient's general health, the discovery of concomitant diseases, good nursing care, occupational therapy, education and other measures to improve the morale. In addition to this he is convinced of the value of arthrodesis. He believes that it is necessary to establish the diagnosis by biopsy but warns of the importance of performing the arthrodesis at once or soon after the exploratory operation to avoid the breaking down of the wound or the formation of sinuses. He describes the operations which he has found most useful in the treatment of various joints as follows:

Spinal Fusion: The Hibbs technic is followed in its essentials. Subperiosteal exposure of the laminas and thorough removal of the attached ligaments are emphasized, as well as removal of as much cartilage as possible from the articulations. Except in the cervical region, where fusion readily takes place, strip grafts from the ilium are used to augment the fusion prepared by chips turned up and down from the laminas or cut from the spinous processes. If the patient's condition is not good, fusion is performed on only one side of the area (hemifusion). The other side is operated on two or four weeks later. If the area to be fused is long, four hemifusions are usually performed.

Sacroiliac Fusion: A truncated block of sacrum, sacroiliac joint and ilium is removed from the posterolateral portion of the ilium. After the sacral bone and joint cartilage are removed, the iliac portion of the block is countersunk across the line of the joint.

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86. Bosworth, D.: Tuberculosis of Osseous System: Tuberculosis Involving Skeleton Other Than Spine, Quart. Bull., Sea View Hosp. **5**:189-220 (Jan.) 1940; Tuberculosis of Osseous System: Complicating Factors in Management of Osseous or Arthrogenic Tuberculosis, ibid. **5**:320-340 (April) 1940; Tuberculosis of Osseous System: Operative Methods, ibid. **5**:441-470 (July) 1940.

Fusion of the Hip: Through an anterior approach, the hip joint is disarticulated, and the remaining cartilage is removed from the head of the femur and the acetabulum. The head of the femur or remnants of the neck are then replaced, and a massive sinuous graft, 3 to 3½ inches (7.5 to 8.9 cm.) long and 1¼ inches (3.2 cm.) wide, consisting of both tables of the ilium, is removed from the crest. The graft is driven into a deep slot running through the ilium anteriorly, across the hip joint and through the head and neck into the shaft of the femur. Cancellous strips may be distributed about the denuded joint margin.

[ED. NOTE: Dislocation of the femoral head, in our opinion, is undesirable, because it destroys any reparative process that may have occurred.]

Femoroischial Fusion: In certain cases in which the head and neck of the femur have been totally destroyed and in which fibrosis has occurred in adduction and flexion, an oblique osteotomy is performed just above the level of the ischial tuberosity. The sharpened femoral stump is then implanted in the ischium. If the proximal fragment of the femur shows active tuberculous infection at the time of dissection, it may be removed. [ED. NOTE: This is an original procedure which should prove useful in the treatment of the advanced conditions for which it was designed.]

Anterior Decompression of the Spine: Most paraplegias associated with tuberculosis of the dorsal region of the spine are due to pressure of granulation tissue or of abscess pocket material extradurally, which is usually relieved as fusion occurs and disease activity subsides. Occasionally, however, such a paraplegia is due to fragmentation of a destroyed body caught between inclined surfaces of the vertebrae above and below and driven backward by the pressure of collapse to compress the spinal cord against the posterior arches. In these cases, the bony fragments, tuberculous granulation tissue and debris are removed by a costotransversectomy after fusion has become solid.

Fusion of the Knee: The method of Hibbs is used, in which the patella is mortised between the denuded ends of the femur and the tibia.

Fusion of the Ankle: A sliding graft from the tibia is moved downward and implanted into the astragalus after all cartilage has been removed from the ankle joint surfaces, including those of the malleoli. [ED. NOTE: This graft technic is not advisable for children in whom the lower epiphysial line of the tibia is still functioning.]

Fusion of the Shoulder: The cartilage is removed from the head of the humerus and the glenoid cavity through a saber cut incision just lateral to the tip of the acromial process. The under surface of the acromion is bared, and the humeral head is held in apposition to it by

two vitallium screws. Bone shavings are placed between the head and the glenoid cavity.

Resection of the Elbow Joint: This is preferred to arthrodesis because of the frequent complaint of the angulation of the upper extremity in cases in which fusion has been done. The joint of the elbow and its capsule and portions of bone about ¾ inch (1.9 cm.) each from the humerus and the forearm are resected through a posterior incision.

Fusion of the Wrist: Through a dorsal incision, curettage of the interarticular facets of the carpal bones and the radiocarpal joints is done as completely as possible. A massive sliding graft is then moved down from the radius and driven into the bases of the metacarpal bones, except the first. Slight dorsiflexing of the wrist holds the proximal end of the graft apposed to the radius. [ED. NOTE: This graft technic is not advisable for children in whom the lower epiphysial line of the radius is still open.]

Amputation: In the lower extremity the Gritti-Stokes amputation with its end-bearing stump is preferred. In the presence of massive tuberculous infections above the knee, midthigh amputations, even performed through purulent areas, have healed surprisingly well.

Amputation in the upper extremity is to be avoided if possible, because the crippling effect is so severe. Intractable pain due to contracting soft tissue, shutting off of the blood supply or complete destruction of a hand has occasionally justified routine amputations at various levels.

The importance of excision of the corresponding metacarpal bone when amputation of a finger is necessary is emphasized; this procedure leaves a better appearing and functioning hand.

Tuberculosis of the Hip.—Borellini [87] has observed 3 cases of tuberculosis of the hip which are of interest because of the unusual locations of the abscesses. In the first case, a girl of 12 had an abscess in the region between the iliac crest and the ribs; several fistulas developed here and in the vicinity of the sacroiliac joint. In another 12 year old girl an abscess and sinus appeared in the lumbosacral region and were traced to a tuberculous focus in the right hip. A boy 15 years of age presented a tuberculous sinus over the sacroiliac joint which was proved to have its origin in the ilium above the left hip.

Wassersug [88] reports 18 cases of tuberculous trochanteric disease, in 16 of which the diagnosis was confirmed. In 5 the trochanter alone was involved; in 2, only the bursas; in the others there was combined

87. Borellini, A.: Ossifluent Abscess: Unusual Evolution in Three Cases, Arch. di med. e chir. **9**:65-76 (Feb.) 1940.

88. Wassersug, J. D.: Tuberculosis of Greater Trochanter and Trochanteric Bursae, J. Bone & Joint Surg. **22**:1075-1079 (Oct.) 1940.

involvement. In 72 per cent there were other demonstrable tuberculous foci. There was a history of local trauma in many. Numerous operations were performed on 15 patients. Incision and drainage alone accomplished no permanent relief and were almost always followed by persistent sinuses. Radical excision or curettage was performed on 10 patients, and on their discharge from the hospital, six to ten months later, there were no draining sinuses or any disability from the lesion. The conclusion was that radical excision was the method of choice for treatment.

Tuberculosis of the Knee.—Haas [89] gives case reports of 12 children between the ages of 2¾ and 12½ years who had fusion of the knee for tuberculosis. It usually required two operations to obtain solid fusion. The children were followed for an average of three and one half years, some of them for seven or eight years. In 8 there was no shortening; in the others there was only ½ inch (1.27 cm.) or less of shortening.

Haas concludes that fusion of the knee can be performed in children as young as 2¾ years without any loss of growth.

Murray [90] made an investigation of 124 cases of tuberculosis of the knee joint picked at random from 2,922 cases of tuberculosis of joints. Biopsy was not done; the diagnosis was made solely on clinical and roentgen examination. All were followed for at least five years.

Thirty-three patients with synovial involvement only were treated conservatively with Thomas splints. Thirty per cent had a full range of motion at the time the study was made. Seventy with involvement of bone were treated first conservatively and then by excision. The operation resulted in ankylosis is only 45 per cent and had a mortality of 21 per cent.

The remaining patients apparently did not have tuberculosis of the knee joint at all but had "extra-articular involvement." [ED. NOTE: Resection of the knee joint is liable to result in extreme shortening of the extremity in a child and, as shown in Murray's cases, is not at all certain to end in fusion. On the other hand, one of us (A. D. S.) has been successful, as was Haas, in obtaining arthrodesis in young children simply by removing the articular cartilage. In some of the cases, however, there was as much as 2 inches (5 cm.) shortening when growth was completed.]

Tuberculosis of the Ankle and Foot.—Mitchell [91] studied the results of treatment of tuberculosis of the ankle and tarsus in 169 patients. The

89. Haas, S. L.: Growth Following Fusion for Tuberculosis of Knee in Children, J. Bone & Joint Surg. **22**:1048-1053 (Oct.) 1940.

90. Murray, R. C.: Tuberculosis of Knee: Follow-Up Investigation of Old Cases, Brit. M. J. **2**:10-12 (July 6) 1940.

91. Mitchell, W. R.: End-Results and Treatment of Tuberculous Disease of Ankle and Tarsus, Brit. J. Surg. **28**:71-81 (July) 1940.

outcome in those under 17 years of age was so different from that in the adults that the two groups were analyzed separately. He divided the 77 children into three groups. In the first two, those with extra-articular and those with synovial tuberculosis, none of whom was operated on, the results all were good. Sinuses developed in 77 per cent of the patients with intra-articular involvements. The treatment was by splints, and in only a few cases, in which operation was performed, was the diagnosis proved. Mitchell states that biopsy is not justified. Of the 45 adults only 12, or 27 per cent, were cured. The results were so bad that he concludes that for adults "conservative treatment should be tried only for a limited period, and if the response is not satisfactory, amputation should be performed without further delay." [ED. NOTE: The statistics of any series of cases in which the diagnosis has not been proved by pathologic examination are of little value, because of the large error which is inevitable. It is our opinion that biopsy in doubtful cases is essential. The results from arthrodesis both in children and in adults have been so satisfactory in the experience of one of us (A. D. S.) that amputation seems justifiable only in an occasional case of severe and advanced involvement.]

Tuberculosis of the Mandible.—Tuberculosis of the mandible is a rare disease. Meng [92] reports 14 cases observed in seventeen and a half years at the Peiping Union Medical College Hospital, Peiping, China. Operative treatment consists of incision and drainage, sequestrectomy and partial ostectomy. There were tuberculous lesions in other bones in 43 per cent of the cases; and in 10 in which the chest was studied there was evidence of pulmonary or pleural tuberculosis. General antituberculous measures in the treatment are emphasized as well as local therapy to the mandibular lesion.

Tuberculosis of the Spine.—The question of spinal fusion as opposed to conservative treatment alone is discussed at length in articles read in a symposium at the meeting of the American Academy of Orthopaedic Surgeons in January 1940.

In speaking of the pathogenesis and medical treatment, Amberson [93] says that in the presence of vertebral tuberculosis a source in the chest should always be assumed and sought for, as well as hematogenous lesions in other systems, such as the serous membranes, the lymphatics and the genitourinary tract.

Treatment is aimed first at arresting hematogenous dissemination, diffusion of toxins from the vertebral lesions and the destructive proc-

92. Meng, C. M.: Tuberculosis of Mandible, J. Bone & Joint Surg. **22**:17-27 (Jan.) 1940.

93. Amberson, J. B., Jr.: Pathogenesis and Medical Treatment of Tuberculosis of Vertebrae, J. Bone & Joint Surg. **22**:807-814 (July) 1940.

esses of caseation and liquefaction. Later, adequate time should be allowed for complete healing, which may require several years. Healing cannot be accelerated materially except by rest treatment given according to its comprehensive meaning. For any form of tuberculosis surgical treatment usually is most effective ultimately, if it is postponed until the forces of resistance have become organized and the lesion has started to heal.

Mayer [94] gives his observations on 66 patients with tuberculosis of the spine who were treated over a period of fifteen years. All were children under 18 years of age. Thirty-seven were treated by spinal fusion and 29 without operation. Mayer states that there was little or no apparent difference in the end results in the two groups except that cure occurred 20 per cent later in those treated by operation. He states that if spinal fusion is done during the active stage of the disease it does not abbreviate the course but that if done during the reparative stage it has a beneficial effect. He believes that the general treatment of the systemic disease is more important than that of the local condition. [ED. NOTE: The conclusions from the study of this relatively small number of cases are contrary to those of the majority of surgeons. Except for 2 cases in which exploration revealed solid fusion, there is no critical study of the number of pseudoarthroses.]

Swett, Bennett and Street [95] give a report of a statistical study of 350 cases of tuberculosis of the spine from four different geographic areas. Patients of all age groups are included. Approximately half the group were treated conservatively. The length of follow-up study was from five to twenty-five years. The authors conclude that:

1. The present treatment of spinal tuberculosis is not satisfactory, because of the low percentage of cures, long duration of treatment and high mortality rate.

2. In general there is no advantage in operative as opposed to nonoperative treatment.

3. The occurrence, behavior and disposal of the abscess are the dominant factors in the healing of Pott's disease. They found that the incidence of healing in all cases was 35 per cent, that in cases with persistent abscess it was 19 per cent and that in cases in which the abscess healed it was 59 per cent. They believe that further progress in the

94. Mayer, L.: Critical Study of Tuberculosis of Spine in Children, J. Bone & Joint Surg. **22**:875-877 (July) 1940.

95. Swett, P. P.; Bennett, G. E., and Street, D. M.: Pott's Disease—Initial Lesion, Relative Infrequency of Extension by Contiguity, Nature and Type of Healing, Role of Abscess, and Merits of Operative and Non-Operative Treatment, J. Bone & Joint Surg. **22**:878-894 (July) 1940.

successful treatment of the disease lies in the better understanding of this factor. [ED. NOTE: This report represents a careful study of a large number of cases. We believe that the value of the conclusions is lessened by the fact that no determination was made of the number of failures of fusion after operation. We are sure that this is necessarily high in any series and that unless these cases are detected and the defect repaired the results cannot be attributed to the method of treatment. Is not the failure of the abscess to disappear the result of the failure of the focus in the bone to heal, rather than the reverse?]

Cleveland [96] compares two groups of patients with tuberculosis of the spine, one treated at Sea View Hospital, a municipal institution on Staten Island, New York, where many patients with severe and advanced tuberculosis are seen, and the other treated at St. Luke's Hospital, New York. In all, there were 203 patients, admitted from 1924 to 1939. At Sea View Hospital the spine was affected in 52 per cent of 330 cases of tuberculous disease of the joints. Of the cases in which the spine was affected there was involvement of other joints in 15 per cent, and in these the results were the least favorable.

Cleveland emphasizes the importance of concomitant pulmonary and other tuberculous lesions in relation to the outcome by citing the mortality rates for various classes of patients as follows: (1) For those with no evidence of pulmonary tuberculosis, the mortality rate is 11.2 per cent; (2) for those with pulmonary tuberculosis but normal sputum and no spread to other organs, 7.2 per cent; (3) for those with pulmonary tuberculosis and evidence of tubercle bacilli in the sputum, 40 per cent; (4) for those with pulmonary tuberculosis and metastatic spread to other organs, 67.7 per cent.

There was the usual failure on the part of the physicians first examining these patients to recognize the disease early. Paraplegia occurred in 48 of 203 patients. Eleven were treated by laminectomy; 6 of these recovered their motor power. Of 31 having complete paraplegia, 42 per cent died.

Abscesses occurred in 68 per cent of 173 cases at Sea View Hospital and in only 23 per cent of 30 cases at St. Luke's Hospital. Roentgen evidence of abscess was present long before clinical signs in a high percentage of the cases. Sinuses were present in 22 per cent of the patients at Sea View Hospital, and 50 per cent of these patients died.

Spontaneous fusion occcurred in 23 per cent of the cases at Sea View Hospital, and in this group the disease had been present for more than six years. In them the deformity usually was marked.

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96. Cleveland, M.: Tuberculosis of Spine: Clinical Study of Two Hundred and Three Patients from Sea View and St. Luke's Hospital, Am. Rev. Tuberc. **41**:215-231 (Feb.) 1940; Treatment of Tuberculosis of Spine, J. Bone & Joint Surg. **22**:824-839 (July) 1940.

The spines of all the patients were fused by the Hibbs type of operation, and frequently reenforcement was provided with bone from the ilium or the tibia. Failure of fusion occurred in 15 of 203 cases, or 7.4 per cent. The importance of looking for this and repairing a defect when found is stressed. The necessity of doing fusion operations on infants and children is urged. Cleveland believes that his statistics prove this to be the treatment of choice for young patients. Fifty-five per cent of the 203 patients had excellent results; in 19 per cent the results were uncertain, and 25 per cent died. The per cent of recovery was higher and that of deaths lower in the patients at St. Luke's Hospital, probably owing to the fact that most of them were in the first two of the classes previously mentioned.

Cleveland points out that patients with active pulmonary disease may be treated by collapse therapy before fusion of the spine. He concludes that fusion of the spine hastens recovery and shortens the course of the disease.

Swift [97] presents a study of 584 patients with tuberculosis who had operations for spinal fusion at the New York Orthopaedic Dispensary and Hospital from 1911 to 1931 and who have been followed from five to twenty-four years or are known to have died. This number represents 71 per cent of the 817 patients with tuberculosis of the spine who were operated on in this period. For 61 per cent the length of follow-up was ten or more years.

Although in every case there are present a group of factors, such as the patient's power of resistance and the degree of virulence of the infecting organisms, that exert an influence on the course of the disease, there are certain demonstrable and expected benefits of a successful fusion. These are: (1) rest of the diseased area (the primary purpose and fundamental result of the fusion); (2) early subsidence of the activity of the lesion; (3) maintenance of the kyphos at a minimum of deformity; (4) growth of the vertebral bodies in the fused area in children to the extent potential in the growth factors which have survived the ravages of this disease; (5) possibility of the patient being ambulatory at an early date (87 per cent were up at the end of four months); (6) a permanent healthy roentgenographic appearance of the diseased vertebrae.

These effects are not observed in every patient. The two chief causes of an unsuccessful outcome are the inability of the patient's tissues to resist tuberculosis and the failure of the fusion to become solid or to

97. Swift, W. E.: End Results of Spine-Fusion Operation for Tuberculosis of Spine, J. Bone & Joint Surg. **22**:815-823 (July) 1940.

cover a sufficient number of vertebrae. Pseudarthrosis occurred in 15 per cent of the cases.

Among the 584 patients there have been 168 known deaths (28 per cent). Fifty-three per cent were caused by some form of tuberculosis. This represents 88 persons and means that 15 per cent of the 584 died of tuberculosis. There were 7 operative deaths from shock, and 1 from shock and a streptococcic wound infection. Calculated on the basis of the 584 patients, the operative mortality was 1.4 per cent.

The patients with successful outcomes were divided into two groups: those who made an early recovery without complication and those who reached an excellent condition only after overcoming various complications, such as failure of the first operation to attain fusion. Of the children, 54 per cent had an early excellent result and 18 per cent, a delayed recovery. Of those over 11 years, 44 per cent had an early and 9 per cent a delayed good result.

The patients were also divided into children (1 to 10 years) and older patients (11 years or over). In both groups (the patients with uncomplicated and those with complicated recoveries) the results for children were better. The combined groups showed excellent results in 72 per cent of the children and in 53 per cent of the older patients.

In writing of the results of treatment of 39 children with tuberculosis of the spine at the Children's Memorial Hospital in Chicago, Chandler and Page [98] emphasized that the disease is a secondary pathologic lesion in a person with tuberculosis, and that healing is variable and dependent on the inherent immunity of the tissues, the reaction of the cellular elements adjacent to the lesion and the physicochemical processes involved in calcification. Recovery should not be referred to as healing, because the latter implies obliteration of the infecting organism. Collapse of the bodies facilitates healing, but an effort is made to keep the deformity at a minimum. Nutritional and hygienic measures are very important, and Chandler and Page wait for improvement in general before operating and stress the general after-care of the patient.

All patients came from unfavorable surroundings, and 36 per cent had a history of contact with a person with tuberculosis at home. Sixty-one per cent had a healed and 12 per cent an active pulmonary lesion. All of the patients were operated on by the Hibbs technic. Twenty-five patients, or 64 per cent, made a good recovery. In 3 the disease remained active. Paraplegia persisted in 1, and 6 died. The end result was unknown for 4.

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98. Chandler, F. A., and Page, M. A.: Tuberculosis of Spine: End Result Series Studied at Children's Memorial Hospital, Chicago, J. Bone & Joint Surg. **22**:851-859 (July) 1940.

The result of fusion of the spine in 396 cases of tuberculosis is given by Meyerding.[99] The patients were treated at the Mayo Clinic. The ages varied from 1 to 60, with the greatest number between 20 and 40. Four per cent were children. Three different types of spinal fusion were employed. All patients were followed for at least five years after operation. Good results were obtained in 63 per cent, all of whom were able to resume some form of occupation. Meyerding believes that spinal fusion combined with adequate conservative treatment is the treatment of choice but that this should not be done in an early stage of the disease, especially in children. He thinks that there is little choice in the methods of spinal fusion so far as the results go. The area fused must include all of the diseased vertebrae.

Harris and Coulthard[100] gave the results of the treatment of 80 patients with tuberculosis of the spine in a hospital for tuberculous patients in Toronto, Canada. Thirty patients were treated by rest alone because they were considered poor surgical risks. In them complications were common, and the mortality was high. The remaining 50 were treated by spinal fusion and rest. The operations were done from six months to three years after the rest treatment was started. Tibial grafts were fixed to the spinous processes by stainless steel wire. Rest in bed was continued for at least six months after operation. Bony ankylosis occurred in 66 per cent. Fracture of the graft occurred in 18 per cent. During the follow-up period, which was comparatively short, 12 per cent died. Ninety per cent of the patients had abscesses treated by repeated aspiration. Thirty per cent of the patients had active pulmonary tuberculosis.

Adams[101] reviewed 63 cases of tuberculosis of the spine treated at the Lakeview State Sanatorium in Middleboro, Mass. All were followed for five years or more. The infections were of both the human and the bovine type, and a limited number of complications in the form of lesions in other organs were present. Debilitated patients were built up before operation. All the patients were operated on, some by the Hibbs technic but the majority by the Albee bone graft. Thirty-eight patients recovered, and twenty-five died. Adams states that for those who did recover the period of healing was long.

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99. Meyerding, H. W.: Tuberculosis of Spine: Treatment and Results, J. Bone & Joint Surg. **22**:840-850 (July) 1940.

100. Harris, R. I., and Coulthard, H. S.: End-Results of Treatment of Pott's Disease, J. Bone & Joint Surg. **22**:862-874 (July) 1940.

101. Adams, Z. B.: Tuberculosis of Spine in Children: Review of Sixty-Three Cases from Lakeville State Sanatorium, J. Bone & Joint Surg. **22**:860-861 (July) 1940.

Rosenbaum [102] gives the result of spinal fusion in 100 cases of tuberculosis in children. He does not state the length of time that the patients were followed after operation. Various operative technics were used. His plan was to give general supportive treatment for a minimum of two years and to perform the operation only after the patient had reached the quiescent or recuperative stage. His results were extraordinarily good, including decrease or arrest of deformity in 94 per cent of the cases, improvement of paraplegia in 76 per cent and healing in 89 per cent.

[ED. NOTE: The number or fate of those patients whose condition did not become quiescent and who therefore were not subjected to operation is not given. We believe that operation should be postponed until the patient's general condition is reasonably good but that to wait until the disease is quiescent is a mistake, because in some cases it never reaches this stage.]

V. INFECTIONS OF BONES AND JOINTS, EXCLUSIVE OF TUBERCULOSIS

General Considerations.—While nontuberculous infections of bones and joints are caused in the main by the staphylococcus and the streptococcus, Valentini [103] points out that there is a variety of less frequently encountered organisms which also may be causes. In the early stages of diseases of bones and joints the clinical features may have certain differences depending on the organism present, but as a general rule roentgenograms will show primarily bone destruction in the tuberculous infection and both bone production and bone destruction in the nontuberculous.

Hanke [104] states that there are two routes of infection, the hematogenous and the exogenous; the former is the more common in peace times. He feels it is important to determine which organism is responsible and points out that in most cases the streptococcus does not produce necrosis, whereas the staphylococcus nearly always produces both necrosis and sequestration.

Toye [105] emphasizes that orthopedic surgeons must become "osteomyelitis conscious." In this way diagnosis can be made earlier and treatment begun before much local bone damage can occur.

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102. Rosenbaum, M. G.: Tuberculosis of Spine, Southwestern Med. **24**:123-125 (April) 1940.

103. Valentini, F. B.: Therapy of Articular Suppurations with Special Reference to Early Form, Policlinico (sez. chir.) **47**:41 (March) 1940.

104. Hanke, H.: Acute Osteomyelitis, Med. Klin. **36**:80-82 (Jan. 19) 1940.

105. Toye, J. E.: Acute Hematogenous Osteomyelitis: Diagnosis and Treatment, J. M. Soc. New Jersey **37**:51-53 (Feb.) 1940.

Le Cocq [106] emphasizes the tendency of the bacteria to lodge in the deeper channels next to the epiphysial line, where phagocytosis is least active.

Rantz [107] reports a case of suppurative arthritis of the knee and the hip due to streptococci of the Lancefield group B, which have rarely been found infecting human beings. He states that the disease usually starts in the metaphysis or cancellous end of the diaphysis, where the circulation is relatively sluggish, and spreads locally to involve the adjacent shaft by stripping the periosteum or, if the epiphysis is intra-articular, perhaps spreads into the adjacent joint.

Martin and Picquart [108] point out that children up to the age of 3 years are particularly susceptible and that the disease in this age group is clinically different from osteomyelitis in adults. They say that epiphysitis is the most characteristic lesion in infancy. The first stage consists of vascular injection of varying duration; suppuration occurs during the second stage with the clinical features of high fever, pain and swelling at or near the joint and evidences of general constitutional toxicity. The disease then erodes into the joint, resulting in deformity and a tendency to pathologic subluxation or dislocation.

Valentini [103] reports 5 cases of acute suppuration of the synovial membrane and states that the joints were involved in the following order: knee, ankle, hip and shoulder. The mortality rate was highest in the cases in which the shoulder was affected.

From a review of the literature Lauber [109] also finds the knee is the most frequently involved. He cites Wiesmann,[109a] who observed that in 52 per cent of his cases the portal of entry was the skin, and in 15 per cent, the tonsils. While various types of organisms may be found as the infecting agent, Hanke [104] feels that other factors play a definite part and that the body's resistance to the disease may be dependent on whether or not there is a deficiency of vitamin C. In addition, there is a physical incidence as well as a geographic distribution, and he treats of the relation of previous trauma to the development of osteomyelitis. He states that trauma can be admitted as a common causative factor only if it is of sufficient severity to produce a manifest injury to the affected bone, and then only if the osteomyelitis develops within twenty-four to seventy-two

106. Le Cocq, J. F.: Diagnosis and Treatment of Acute Osteomyelitis, Northwest Med. **39**:171-172 (May) 1940.

107. Rantz, L. A.: Suppurative Arthritis Due to Hemloytic Streptoccocus of Lancefield Group B: Case Report, Ann. Int. Med. **13**:1744-1747 (March) 1940.

108. Martin, A., and Picquart, A.: Osteomyelitis in Children, Semaine d. hôp. de Paris **16**:58-64 (March) 1940.

109. Lauber, H. J.: Therapy of Empyema of Knee with Review of Literature, Med. Klin. **36**:360-361 (March 29) 1940.

109a. Wiesmann, E.: Problem of Pyemic Metastases into Joints, Deutsche Ztschr. f. Chir. **249**:224-255, 1937.

hours after the trauma. Colonna [110] feels that in acute hematogenous osteomyelitis the disease in the bone is always secondary to an infection elsewhere in the body.

Bordasch [111] has studied the bactericidal power of bone marrow under the influence of external agents in his experiments on rabbits, and he concludes that a blunt injury of the shaft of a long bone produces a marked and prolonged increase in the bactericidal power of the bone marrow at this site. He states that the bactericidal power of the bone marrow in any part of the body is considerably greater after hemorrhage than after trauma to a bone and about twenty times greater after hemorrhage than when the marrow is normal. These interesting experiments led him to conclude that in cases of extreme malnutrition and starvation the bactericidal power of the bone marrow is increased even more than after hemorrhage and is about thirty times more than that of normal bone marrow.

Rosenbach [112] has found that trauma is an infrequent cause of osteomyelitis; although clinical observations may disclose injury as a frequent precursor, an actual source of infection, such as an open fracture, a furuncle or an infected wound, must be demonstrated. However, he reports 2 cases in which trauma alone seemed to be the initiating factor. One patient was a boy who injured both knees while exercising; osteomyelitis developed in both tibias a few days later. In the second case there was an injury to the ankle, and fourteen days later osteomyelitis developed in the lower end of the tibia. The criteria of traumatic osteomyelitis, he states, have been laid down by Liniger and are as follows: (1) The accident must be demonstrated; (2) there must have been considerable action on the subsequently diseased bone; (3) the disease must have originated in immediate association with the injury. Therefore, it is obvious that the relation of trauma to osteomyelitis can seldom be clearly demonstrated.

Beekman and Sullivan [113] feel that every attempt should be made to recognize the type of organism causing the infection before treatment is begun, as streptococcic septicemia behaves differently from staphylococcic in both its general and its local reactions. Because one is dealing with a bacteremia in these cases, the best results are obtained when the lesions of bones and joints are treated by conservative surgical measures

110. Colonna, P. C.: Acute Hematogenous Osteomyelitis, J. Kansas M. Soc. **40**:493-498 (Dec.) 1939.

111. Bordasch, F.: Experimental Study of the Bactericidal Effect of Bone Marrow, Deutsche Ztschr. f. Chir. **253**:237-262, 1940.

112. Rosenbach: Osteomyelitis and Trauma, Monatschr. f. Unfallh. **46**:597-605 (Dec.) 1939; abstracted in Painter, C. F.: Year Book of Industrial and Orthopedic Surgery, Chicago, The Year Book Publishers, Inc., 1940, p. 38.

113. Beekman, F., and Sullivan, J. E.: Blood-Borne Pyogenic Infections of Bones and Joints, Ann. Surg. **111**:292-314 (Feb.) 1940.

alone and more attention is paid to the general condition of the patient and supportive measures employed. [ED. NOTE: We are in complete agreement.] In their 21 cases of pyarthrosis in acute osteomyelitis, aspiration of the joint one or more times or incision to relieve tension, immobilization of the extremity and infrequent dressings proved to be of decided benefit.

McCoy and Ross [114] feel that in cases of acute hematogenous osteomyelitis the prognosis can be based on the presence or absence of a positive blood culture, on the type of organism found and on the number of colonies found if the blood culture is positive. In addition to surgical drainage and immobilization, the administration of staphylococcic antitoxin is recommended by these authors. While in the average case osteomyelitis develops in the metaphysial region of the bone, Paltrinieri [115] describes cases of chronic diaphysial osteitis of the bone and states that this condition may begin in childhood or adolescence with a deep severe pain, usually in one of the long bones and associated with more or less circumscribed tumefaction. In diaphysial involvement, the organism is usually the staphylococcus and the typical lesion is a small excavation of the cortex, which is filled with pus and sometimes contains a small sequestrum. This condition must be differentiated from tuberculosis, typhoid or Ewing's bone tumor.

Brodie's Abscess.—Cousineau [116] reviews in detail the condition first described by Brodie and since known as Brodie's abscess. Cousineau states that in 1765 Davis described what was probably the same condition. Brodie's abscess is a local chronic bone abscess. It occurs mostly in persons under 15 years of age during the period of active growth. Boys are more frequently affected than girls; in order of frequency the bones affected are the lower end of the femur, the humerus and the radius. Trauma must be a very real factor in the production of the abscess. The cavity has usually been found to contain staphylococci, but typhoid and colon bacilli have been isolated. Cousineau points out that many times the contents are sterile. The treatment recommended is opening the wound and cleaning it out thoroughly; then it is tightly closed.

Sclerosing Osteitis of Garré.—Another form of infection of bones is the chronic, diffuse sclerosing osteitis of Garré, which is described by Toumey.[117] This condition manifests itself by a dull ache in the region

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114. McCoy, R. H., and Ross, D. E.: Acute Hematogenous Osteomyelitis, Canad. M. A. J. **42**:162-168 (Feb.) 1940.

115. Paltrinieri, M.: Circumscribed Cortical Osteitis, Chir. d. org. di movimento **25**:407-416 (April) 1940.

116. Cousineau, P.: Brodie's Abscess, Ann. méd.-chir. de l'Hôp. Sainte-Justine, Montreal **3**:145-154 (May) 1940.

117. Toumey, J. W.: Sclerosing Osteitis of Garré, S. Clin. North America **20**:857-861 (June) 1940.

involved, usually worse at night. It should be differentiated from syphilitic periostitis, osteogenic sarcoma, Ewing's sarcoma and hyperparathyroidism. Dusting sulfanilamide powder into the saucerized wound followed by complete closure is recommended.

Syphilis.—Evans [119] discusses syphilis of bones and joints in infants. He feels that the diagnosis of congenital syphilis may be difficult to make and that in most cases it is either finally confirmed or excluded by serologic studies or by roentgen examination of the long bones. A positive reaction, he states, is of doubtful validity, as it is known that the property of producing a positive reaction may be transferred from the maternal blood to the fetal blood without the fetus being syphilitic. On the other hand, the negative serologic reaction of a newborn child is also inconclusive, for many children who eventually show evidence of syphilis have negative serologic reactions at birth.

Evans also points out that bands of rarefaction or condensation in the diaphysis are frequently seen in roentgenograms, especially in those of premature infants and ones with nutritional disturbances. These cannot, however, be regarded as specific for syphilis. The periosteal shadows, varying from a fine white line parallel to the long bones and most commonly observed in the femur to heavy onion-like cloaking of the bone, have been considered in the past as pathognomonic of syphilis, but Evans feels that they are not, as these appearances may be found in subperiosteal fractures occurring at delivery. Rickets, tuberculosis and other forms of osteomyelitis make the diagnosis of congenital syphilis difficult.

McDonald and Sellers [120] feel that roentgenograms will detect syphilis of the bone in most cases by the time the infant has reached the age of 6 weeks. Hill in discussing this paper says that the roentgenographic characteristics of congenital syphilis, namely, periostitis and destruction in the ends of bones along with smooth, condensed and irregular epiphysial lines, should not be confused with the signs of either scurvy or rickets. Scurvy will not show changes in the bones before the fifth month and therefore need not be considered at all during the first two months. Brown in this same discussion says that, while there is always multiple osseous involvement, not all the bones are affected. Therefore, he advises a study of the whole bony system in every case; this in his opinion would permit congenital syphilis to be discovered within the first two or three months of life.

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118. Footnote deleted by author.

119. Evans, W. A., Jr.: Syphilis of Bones in Infancy: Some Possible Errors in Roentgen Diagnosis, J. A. M. A. **115**:197-200 (July 20) 1940.

120. McDonald, D. H., and Sellers, E. D.: Pulmonary and Bony Changes in Congenital Syphilis, Texas State J. Med. **35**:838-840 (April) 1940.

Thomason and Mayoral [121] state that syphilitic periostitis is usually a secondary or tertiary phenomenon and seldom occurs before two years after the initial infection. However, some authors have described it as occurring at the same time or from two to fifteen weeks after the infection. Syphilitic periostitis according to Thomason and Mayoral affects primarily adults between the ages of 20 and 40; the shafts of the long bones and the outer table of the skull are most frequently involved. The disease may be congenital, but this is not the usual form. In patients with osseous lesions injection of arsphenamine is followed by intense pain for twelve to twenty-four hours and then prompt relief, perhaps the first in months. If, however, the whole bony structure is involved rather than the periosteum only, the disappearance of the signs and symptoms may be much more gradual and require days or weeks, during which there will be little if any objective change in the osseous lesions. The patient with syphilitic infection of bones should be kept under observation indefinitely, and special emphasis must be placed on periodic examinations of the heart and aorta as long as the patient lives.

In discussing syphilis of the joints, Freund [122] stresses the intra-articular hemorrhage and effusion that may be produced in the joint, stating that the normal joint pressure is negative but that under certain conditions it may increase to a positive value of 70 mm. of water. This, he says, will cause injury to the underlying bone, particularly hemophilic arthritis, in which there may be destruction of the whole epiphysis.

Gandola [123] reports syphilitic tenovaginitis in a man of 30 with a noncontributory family history who had suffered for one month from a lesion of the prepuce and during the second stage from a swelling of the right hand and forearm. After treatment for a few days with an insoluble bismuth preparation the patient improved and after the second injection became well. The symptoms subsided in less than one month.

Fungous Infections.—Krumdieck and Stevenson [124] report 1 case of actinomycosis characterized by spinal epidural abscess. Postmortem examination revealed the abscess involving the right side in the thorax, the chest, the vertebrae and the liver. Hurst [125] reports a case of actinomycosis involving the retina, the lungs and the vertebrae. The diagnosis in this case was not made until autopsy, although the sulfur granules

121. Thomason, H. A., and Mayoral, A.: Syphilitic Osteomyelitis, J. Bone & Joint Surg. **22**:203-206 (Jan.) 1940.

122. Freund, E.: Pathologic Significance of Intra-Articular Pressure, Edinburgh M. J. **47**:192-203 (March) 1940.

123. Gandola, M.: Tendovaginitis in Secondary Period, Gazz. d. osp. **61**:243-245 (March) 1940.

124. Krumdieck, N., and Stevenson, L. D.: Spinal Epidural Abscess Associated with Actinomycosis, Arch. Path. **30**:1223-1226 (Dec.) 1940.

125. Hurst, J. H.: Actinomycosis Progressively Involving Retina, Lungs and Vertebrae, M. Bull. Vet. Admin. **17**:90-92 (July) 1940.

were found in the pus discharged from the sinus. He feels there is little evidence that actinomycosis is contagious and believes the infection takes place by implantation of the parasite in the tissues by a foreign body, it being widespread among cattle and pigs. He says statistics indicate that the disease is prevalent in the upper part of the Mississippi Valley and the northwest section of the United States. Craig, Dockerty and Harrington [126] discuss a case of intravertebral and intrathoracic blastomycosis.

Undulant Fever.—Steindler [127] in discussing the orthopedic complications of undulant fever states that one may divide the metastatic lesions of the locomotor system into three groups: those of pyogenic character involving a single joint, those of the serous type with polyarthritic dissemination and those with osteomyelitis. All brucellar lesions are late sequelae of the infection, occurring eight to twelve weeks after the acute onset and having a definite tendency to self limitation. Osteomyelitis of the vertebra is by far the most frequent complication, usually involving the lumbar portion of the spine. Steindler states that up to 1939, 57 cases were reported in the literature, and he adds 4 more. The characteristic features of the skeletal involvement in brucellosis are: preference for the lumbar region of the spine with narrowing of the joint spaces and some reactive bone production; rarity of formation of abscesses; a rather benign course, and response to conservative treatment by rest and immobilization. An enlarged spleen, a low white blood cell count, negative tuberculin and Wassermann reactions and a history of remittent fever, chills and sweating are of importance in the differential diagnosis. A positive agglutination for Brucella in the higher dilutions will usually be observed.

Echinococcic Cyst.—Among the rare nontuberculous infections involving the joints and soft tissues is that caused by Echinococcus granulosus. Mason [128] reports a case of recurring echinococcic cyst of the thigh and states that one of the sources of this infestation is the hands. These are soiled in petting an infected dog that has become contaminated by eating the viscera of a sheep, an ox or a pig. In this way the covered eggs are swallowed. After these eggs bore through the intestinal wall, they get into the portal circulation and finally reach the pulmonary circulation. He believes that infestation occurs in childhood in a great majority of cases and that the cyst may thus be nearly

126. Craig, W. M.; Dockerty, M. B., and Harrington, S. W.: Intravertebral and Intrathoracic Blastomycoma Simulating Dumb-Bell Tumor, South. Surgeon **9**:759-766 (Oct.) 1940.

127. Steindler, A.: Orthopedic Complications of Brucellosis, J. Iowa M. Soc. **30**:256-257 (June) 1940.

128. Mason, J. B.: Recurrent Echinococcus Cyst of Thigh, Surgery **7**:407-409 (March) 1940.

as old as the patient. Diagnosis is easy when an echinococcic epidemic occurs. Mason feels that roentgenograms combined with the complement fixation test of Fairley are useful in the diagnosis. Treatment is unsatisfactory, although complete removal of the cyst is the method of choice.

Lesions of the Vertebra.—In the discussion of osteomyelitis involving the vertebrae, Alexander [129] reports cases in which it occurred in the cervical region and maintains that it is more common than ordinarily supposed. He feels that men have osteomyelitis in the cervical vertebrae twice as frequently as women and that it is found in the second and third decades especially. The causative organisms are chiefly Staphylococcus aureus, Staphylococcus albus and Streptococcus pyogenes. Schein [130] describes a case in which Bacillus pyocyaneus was the positive organism. The infection occurred after a cystoscopic examination. Schein feels that while this organism is generally only mildly pathogenic it may become a dangerous invader after instrumentation of the genitourinary tract. Immobilization by a plaster jacket and chemotherapy were used in the treatment, and apparently the condition was cured. Sacrococcygeal osteomyelitis is described by Bacon and Taylor,[131] who report 2 cases in which the condition simulated anorectal fistula. The best treatment, according to them, consists of removal of the involved bones with wide exposure, the large wound being allowed to granulate slowly. Mathe [132] discusses osteomyelitis of the pelvic girdle. In the case he reports there was an associated vesical fistula. He considers the genitourinary problem involved in the management of such a case greatly complicated whenever intractable cystitis is present.

Syphilitic lesions of the spine are rare and may be mistaken for Pott's disease. Weber and Carrión [133] report a case of syphilitic spondylitis. The patient was a man of 30 with a paravertebral abscess and with roentgenographic evidence of destruction of bone. Two years later a draining sinus developed in the neck, and roentgen examination showed destructive osteitis of the body of the atlas. Weber and Carrión point

129. Alexander, R. J.: Chronic Osteomyelitis of Cervical Vertebrae, Rocky Mountain M. J. **37**:753-757 (Oct.) 1940.

130. Schein, A. J.: Bacillus Pyocyaneus Osteomyelitis of Spine: Report of Case of Successful Treatment with Sulfanilamide, Arch. Surg. **41**:740-746 (Sept.) 1940.

131. Bacon, H. E., and Taylor, A.: Osteomyelitis of Coccyx and Sacrum with Sinus Formation Simulating Ano-Rectal Fistula: Report of Two Cases, New England J. Med. **223**:668-671 (Oct. 24) 1940.

132. Mathe, C. P.: Management of Intractable Cystitis Associated with Vesical Fistula and Osteomyelitis of Pelvic Girdle: Report of Three Cases Following Traumatic Rupture of Bladder and Fractured Pelvis, J. Urol. **43**:543-560 (April) 1940.

133. Weber, L. A., and Carrión, C. J.: Case of Syphilitic Spondylitis of Cervical Spine, Semana méd. **1**:94-97 (Jan. 11) 1940.

out that Wassermann and Kahn tests should always be done in any case in which there is a destructive spinal lesion, and in their case a Calot jacket and specific treatment sufficed to cure the patient after two years.

Lesions of Femur.—Moss [134] discusses osteomyelitis of the femur and reports 11 cases of acute osteomyelitis of the femoral neck, in 7 of which there were the clinical signs of pain on pressure just below the midline of Poupart's ligament and associated with a flexion of the right thigh on the abdomen with a limited range of pain-free motion in the hip joint proper.

Cysts may develop in the popliteal space owing to chronic osteomyelitis of the femur. Borellini [135] reports such an occurrence in a woman aged 30. The disease manifested itself at the age of 6. At this time the knee became swollen without apparent cause, and there was severe and continuous pain. After about a month the patient became symptom free. Many years later the pain reappeared, and a tumor, which was the size of an orange and red and painful to touch, formed on the internal surface of the right knee. Aspiration revealed a yellowish fluid; bacteriologic tests were negative, and roentgenograms revealed chronic osteomyelitis of the right femur. After incision and drainage with curettage of the bone, primary healing occurred.

Mazzini and Carman [136] report a case of brucellosis and state that involvement of joints is far more common than osteomyelitis. They believe this is the first reported case from Argentina. Their patient had worked a number of years in the meat-packing industry. After a cut on his finger, a local infection developed, from which he completely recovered, although he was proved to have undulant fever. Three months later osteomyelitis of the femur developed; culture yielded Brucella suis. This case is of further interest because under the workmen's compensation law of Argentina brucellosis is considered an occupational disease and therefore the patient is entitled to compensation.

Lesions of the Knee.—Lauber [109] discusses suppurative arthritis of the knee joint. He feels that while the staphylococcus is the most frequent offender the streptococcus or practically any of the other organisms may occasionally be the cause. While he reviews the different types of treatment, he advocates conservative expectant treatment; however, all periarticular abscesses should be incised. If arthrotomy becomes necessary the author holds that drainage should be extra-articular and that

134. Moss, W.: Osteomyelitis of Upper End of Femur: Description of Diagnostic Sign, New Orleans M. & S. J. **92**:569-572 (April) 1940.

135. Borellini, A.: Cysts of Popliteal Space Due to Chronic Osteomyelitis, Arch. di med. e chir. **9**:289-296 (June) 1940.

136. Mazzini, O. F., and Carman, D. R.: Brucella Osteomyelitis of Femur, Prensa méd. argent. **27**:517-520 (March 6) 1940.

the use of an iodoform gauze pack or any foreign body in the joint should be strongly discouraged.

Kendrick [137] reports favorable treatment of a patient with septic arthritis of the knee joint by the oral administration of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) combined with multiple aspirations of the joint. The patient was a boy of 14 years of age. The blood and synovia were positive for Staph. aureus, and sulfapyridine was found to be much more effective than sulfanilamide in fighting the infection. This patient left the hospital on the twenty-eighth day with a full range of motion and no tenderness.

Henson [138] recommends the use of oxygen in preventing adhesions in acute infections of joints. He advises withdrawing as much fluid as possible and allowing the oxygen to flow into the joint to the point tolerated by the patient. Compression is maintained several minutes at the point where the needle is removed to prevent the escape of oxygen. He reports that no accident of any kind occurred in his series of 150 cases.

Beutel [139] describes a case of gumma of the patella in a woman of 48 who had injured her knee five years before. She had a strongly positive Wassermann reaction. A shallow impression with a light area of sclerosis and annular hyperostosis were noted in the patella.

Lesions of the Leg.—In a discussion of osteomyelitis of the tibia it should be mentioned that Weaver and Francisco [140] point out that in their opinion the pseudofracture of the tibia, described in 1939 by Roberts and Vogt,[141] should not be called a fracture. They report 3 of their own cases and feel that from the history, physical findings, roentgen and pathologic reports their cases are consistent with a type of nonsuppurative osteomyelitis. Nédelec [142] reports a case in which there was subperiosteal resection of the entire tibial diaphysis for osteomyelitis. The patient was a child of 10 who showed no signs of bone regeneration.

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137. Kendrick, J. I.: Staphyloccocus Septicemia with Septic Arthritis of Knee Treated with Sulfapyridine: Report of Case, Cleveland Clin. Quart. **7**:35-36 (Jan.) 1940.

138. Henson, J. B.: Use of Oxygen in Preventing Adhesions from Trauma and Infection, South. M. J. **33**:776-778 (July) 1940.

139. Beutel, A.: Gumma of Patella, Fortschr. a. d. Geb. d. Röntgenstrahlen **11**: 591-592 (Oct.) 1939; abstracted in Painter, C. F.: Year Book of Industrial and Orthopedic Surgery, Chicago, The Year Book Publishers, Inc., 1940, p. 48.

140. Weaver, J. B., and Francisco, C. B.: Pseudofractures: Manifestation of Non-Suppurative Osteomyelitis, J. Bone & Joint Surg. **22**:610-615 (July) 1940.

141. Roberts, S. M., and Vogt, E. C.: Pseudofracture of Tibia, J. Bone & Joint Surg. **21**:891-901 (Oct.) 1939.

142. Nédelec: Diaphysial Resection in Osteomyelitis: Pseudoarthrosis Treated by Hahn-Hutington Operation, Mém. Acad. de chir. **66**:316-320 (March 13-April 3) 1940.

Accordingly, a Hahn-Hutington operation was done; it consisted of osteotomizing the fibula above and below and grafting it to the tibia to fill the defect. Three years after the operation the result was satisfactory, in spite of shortening of 2 cm. and some laxity of the knee joint. The transplant gradually assumed the dimensions and position of the tibial diaphysis. Nédelec feels that with a large defect the Albee graft is more efficient and should be tried first, but using the fibula and liberating it at both ends instead of only one is recommended. Lenggenhager,[143] in discussing osteomyelitis of the fibula which gives rise to a deformity of a foot after excessive isolated growth of this bone, recommends extirpation of the distal portion of the fibula to correct the deformity.

Lesions of the Jaws.—Padgett [144] analyzes 59 cases of osteomyelitis of the jaws uncomplicated by fracture and states that frank osteomyelitis of these bones is not common. He found that in over one third of the patients the disease was associated with peridental infection, and in 11 of his cases the disease was associated with the result of an extraction during the acute stage of pulpitis or a peridental infection. It is probable that dentists as a rule do not extract a tooth during the acute stage. Nine of these cases in the total series were due to syphilis; this would seem to be rather high. A warning should be given against excessive irradiation in cases of infection of the jaw which in this series was thought to account for 6 cases. Whether a tooth should be extracted during the acute stage of peridental infection is a question of great importance. Padgett says that if the tooth can be simply and easily lifted out of its socket extraction can be generally beneficial. On the other hand, if considerable trauma is necessary for the removal of the tooth it would be somewhat similar to doing a radical procedure early in the course of osteomyelitis elsewhere, a procedure long thought to be distinctly contraindicated.

Fisher and Wallace,[145] after reviewing the literature on pathologic fractures of the mandible, state that prophylactic splinting of all patients with fractures is advisable and may prevent a subsequent fracture. To restore continuity and to bridge gaps in cases of old inactive osteomyelitis, they recommend the bone graft procedure. Jacques [146] in discussing

143. Lenggenhager, K.: Surgical Correction of Foot Deformity Due to Extirpation of Distal Portion of Fibula, Schweiz. med. Wchnschr. **70**:276-277 (March 30) 1940.

144. Padgett, E. C.: Osteomyelitis of Jaws: Analysis of Fifty-Nine Patients, Surgery **8**:821-831 (Nov.) 1940.

145. Fisher, A. F., and Wallace, W. R. J.: Pathologic Fractures of Mandible Predisposed by Osteomyelitis: Report of Case, Am. J. Orthodontics **26**:896-900 (Sept.) 1940.

146. Jacques, P.: Osteitis Invading Upper Jaw, Refractory to Surgery and Cured by Sulfapyridine (Sulfanilamide Derivative), Oto-rhino-laryng. internat. **23**: 465-467 (Sept.) 1940.

osteitis of the upper jaw recommends the use of sulfapyridine and reports a case in which cure was effected by conservative means.

Lesions of the Clavicle.—Yang [147] reviews the literature and reports 6 cases of late congenital syphilis of the clavicle, pointing out that there is an enlargement of the sternal extremity and roentgenographic evidence of a thickening in the bone caused by hyperostosis. He says that the enlargement usually occurs unilaterally on the right side and believes that this is because in embryologic life the inner third of the clavicle is formed directly from connective tissue without the preformation of cartilage and therefore from tissue that is supposed to be infected. The infection remains latent locally, but when puberty sets in the increased activity of the person causes increased movements of the clavicle, leading to hypertrophy of its sternal end. This hypertrophy, he feels, is a practical and convenient sign for physicians to keep in mind as a guide in the diagnosis when there is a negative serologic reaction but there are other evidences of congenital syphilis, and he regards this as a finding of great diagnostic value.

Complications.—Dube [148] says that when the disease involves one or more growing centers all bone growth is often disturbed, and this gives rise to both deformed and shortened bones. He feels it would be of great advantage if one could find a method of treating the general infection and abstaining from all surgical intervention. Of over 2,000 cases of acute hematogenous osteomyelitis at the Mayo Clinic, Macey [149] states that in 66 there was both clinical and roentgenographic evidence of epiphysial changes after osteomyelitis. West [150] points out the fact that osteomyelitis is the cause of crippling in children and that it is one of the most serious diseases known. Davis [151] discusses some of the sequelae of arthritis and osteomyelitis and points out that gonorrheal arthritis, once it is healed, does not recur after operative trauma. In comparing purely suppurative arthritis when healed with hematogenous osteomyelitis, he points out that only 13 per cent of cases of purely suppurative arthritis recurred when operation was performed through the previously

147. Yang, K. L.: Clavicle Sign of Late Congenital Syphilis: Review of Literature and Report of Six Cases, Arch. Dermat. & Syph. **41**:1060-1065 (June) 1940.

148. Dube, E.: Late Results of Chronic Osteomyelitis in Children, Ann. méd.-chir. de l'Hôp. Sainte-Justine, Montreal **3**:35-52 (May) 1940.

149. Macey, H. B.: Epiphyseal Changes Resulting from Acute Infections of Bone, Am. J. Surg. **50**:239-248 (Nov.) 1940.

150. West, W. K.: Osteomyelitis as Cause of Crippling in Children, J. Oklahoma M. A. **33**:13-14 (Oct.) 1940.

151. Davis, J. B.: Recurrence of Infection After Elective Operations in Cases of Healed Suppuration in Bones and Joints, Arch. Surg. **41**:1426-1436 (Dec.) 1940.

involved area. However, in cases of hematogenous osteomyelitis 46 per cent of the recurrences followed subsequent surgical intervention through the involved area. He feels that the complication of recurrence is a major difficulty and should be avoided whenever possible and that by a careful analysis of the roentgenogram of healed osteomyelitis it is possible to anticipate which infections will occur in the event that operation becomes necessary to correct deformity. [ED. NOTE: We think his waiting period is not long enough; he states that six months should be a sufficient interval to make operation safe.]

Therapy.—Dunkmann [152] believes that cases of purely traumatic osteomyelitis are rare, that the prognosis must be regarded as serious in all stages, that combined methods of treatment are advisable and that vaccine therapy is not generally accepted. In general he states that long suppuration presents a continuous menace and that many complications may occur. He reports 314 cases.

Goldman [153] raises the question whether early intervention for osseous lesions of osteomyelitis may not interfere with the development of the body's resistance to the general infection which is always present. In the treatment, as he points out, one has both to combat septicemia and to attempt to preserve the function of the limb. In those cases in which a conservative operation, such as incision or aspiration may not suffice, trephination is recommended, but he feels that it is unnecessary in some cases that tend to heal spontaneously after vaccine therapy or simple incision. He feels that the two prime requisites of therapy are maintenance and stimulation of the general condition and evacuation of the purulent focus when it has become clearly defined.

Phemister [154] discusses the therapy of osteomyelitis. He says that the portal of entry of the organism cannot be detected in 75 per cent of the cases but that in the other 25 per cent it is known to be a local infection, usually of the skin and less often of the respiratory tract. Osteomyelitis as a part of a widespread sepsis does not call for operative treatment but should be treated by administration of fluids, blood transfusion and some form of chemotherapy. Patients with primarily hematogenous severe osteomyelitis fall into two age groups, children and adults. In infants and young children osteomyelitis is due to the hemolytic streptococcus in about 50 per cent of the cases and is often

152. Dunkmann, G.: Osteomyelitis and Its Prognosis, Ergebn. d. Chir. u. Orthop. **32**:527-565, 1939; abstracted in Painter, C. F.: Year Book of Industrial and Orthopedic Surgery, Chicago, The Year Book Publishers, Inc., 1940, p. 36.

153. Goldman, J.: Recent Data on the Therapy of Osteomyelitis, Clinique, Paris **35**:39-40 (April) 1940.

154. Phemister, D. B.: Modern Treatment of Pyogenic Osteomyelitis, Bull. New York Acad. Med. **16**:20-23 (Jan.) 1940.

localized at the end of the shaft, although multiple involvement is common. He is opposed to the use of vaccine, serum, maggots or bacteriophage, for he does not think these have proved sufficiently practical.

De Marchi [155] is one of the few authors who advises early diaphysial resection in cases of acute osteomyelitis; Nédelec [142] advises diaphysial resection at a somewhat later date.

MacNeal [156] in a series of 12 cases of osteomyelitis in which the blood cultures yielded staphylococci used asparagine bacteriophage in adequate doses intravenously. Only 1 patient died. This 8.3 per cent mortality is sufficiently lower than that in his previous experience, and he feels that this bacteriophage has favorably influenced the course of the disease in these patients.

Butler [157] reviews 500 cases of acute hematogenous osteomyelitis and holds that in general one should combat the toxemia, the bacteremia and the local lesion. From a study of 36 consecutive unselected cases of septicemia due to Staph. aureus and treated with bacteriophage, Longacre [158] is of the opinion that when the potency of the bacteriophage is improved and the amount increased the results are much better. He concludes from the results obtained in this series that use of this double potency bacteriophage offers a favorable prognosis to patients infected by Staph. aureus.

Robinson [159] recommends the application of ammonium bicarbonate to the purulent infected wound in a 1 to 2 per cent sterile solution on gauze packs. He feels the occurrence of this compound in the secretion of the maggots is associated with the presence of the enzyme urea in the tissues of the maggots. It is an inexpensive drug and easily prepared in solution.

In writing of some of the complications of osteomyelitis, Forrester [160] considers bone sinuses and their treatment. He recommends the Morrison method. It consists of removal of all dead bone and saucerization of the involved bone. The cavity is then saturated with full strength

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155. de Marchi, E.: Early Diaphyseal Resection in Acute Osteomyelitis, Chir. d. org. di movimento **25**:376-390 (April) 1940.

156. MacNeal, P. S.: Use of Asparagin Bacteriophage in Treatment of Acute Hematogenous Osteomyelitis, Surg., Gynec. & Obst. **71**:766-769 (Dec.) 1940.

157. Butler, E. C. B.: Treatment, Complications, and Late Results of Acute Hematogenous Osteomyelitis Based on Study of Five Hundred Cases Admitted to London Hospital During Years 1919-37 (Hunterian Lecture, Abridged), Brit. J. Surg. **28**:261-274 (Oct.) 1940.

158. Longacre, A. B.; Jern, H. Z., and Meleney, F. L.: Treatment of Staphylococcus Septicemia with Bacteriophage, Surg., Gynec. & Obst. **70**:1-11 (Jan.) 1940.

159. Robinson, W.: Ammonium Bicarbonate Secreted by Surgical Maggots Stimulates Healing in Purulent Wounds, Am. J. Surg. **47**:111-115 (Jan.) 1940.

160. Forrester, C. R. G.: Bone Sinuses and Their Treatment, Am. J. Surg. **50**: 523-524 (Dec.) 1940.

alcohol, and after the wound is dry, a bismuth-iodoform paste is applied to all bone and muscle tissue. The paste is then covered with a transplant of fat, so the wound is closed without tension. The formula he recommends for the paste is 1 part bismuth subnitrate and 2 parts iodoform with sufficient liquid petrolatum to make a thick paste.

Of the complications to be watched for in osteomyelitis of the bones and joints are pathologic fractures with subsequent dislocation of the involved joint; for this reason Nicholson [161] stresses the importance of immobilization of the joint early in the disease to lessen the opportunity for dislocations. General toxemia must be combated and adequate drainage obtained. He feels that sulfanilamide and sulfapyridine have proved of great value. He cautions against early weight bearing and stresses the value of careful follow-up in cases of septic arthritis.

Valentine and Butler [162] have investigated the degree of immunity in patients with recurrence of infection after war wound osteomyelitis and recommend the use of toxoid. The dosage is gradually built up in weekly injections until the patient can take a maintenance dose of 0.3 cc. of undiluted toxoid intramuscularly in the deltoid muscle. However, they say there has not been time to evaluate this treatment with reference to preventing further recurrence.

In the preliminary report, Marcus and Groh [163] recommend the use of roentgen therapy in the treatment of acute osteomyelitis of the fingers and toes. They report 10 cases of infection and osteomyelitis of the phalanges. They believe the response to roentgen treatment is prompt, and early treatment will often prevent complicated osteomyelitis.

VI. CHRONIC ARTHRITIS

Gold Salts.—Numerous preparations of gold salts for the treatment of chronic arthritis have been receiving much critical appraisal from investigators and members of clinic staffs in many lands.[164] The purpose

161. Nicholson, J. T.: Septic Arthritis of Hip: Treatment by Immobilization, Pennsylvania M. J. **43**:950-955 (April) 1940.

162. Valentine, F. C. O., and Butler, E. C. B.: Toxoid Treatment of Recurrent Infection After Staphylococcal Osteomyelitis, Lancet **1**:914-917 (May 18) 1940.

163. Marcus, A., and Groh, J. A.: X-Ray in Treatment of Acute Osteomyelitis of Fingers: Preliminary Report, Indust. Med. **9**:551-554 (Nov.) 1940.

164. (*a*) Osgood, R. B.: Medical and Social Approaches to the Problem of Chronic Rheumatism, Am. J. M. Sc. **200**:429-445 (Oct.) 1940. (*b*) Ruiz Moreno, A.: Chrysotherapy of Rheumatoid Arthritis: Indications and Technic, Arch. urug. de med. **16**:301-312 (April) 1940. (*c*) Mester, A.: Chrysotherapy of Chronic Polyarthritis, Rev. argent. de reumatol. **4**:290-293 (Jan.) 1940. (*d*) Hoegh-Guldburg, O.: Sodium Gold Thiosulfate in Chronic Polyarthritis in Rural Practice, Ugesk. f. læger **102**:500-505 (May 16) 1940. (*e*) Raymundo, B. A.: Gold Salts in Arthritis, An. Inst. modelo de clín. méd. **19**:140-163, 1939.

has been either to find a nontoxic salt [165] or to protect the patient from the dangerous toxic effects of the gold. Liver extract, vitamin C [166] and variation of the amount of the doses of gold salts have been tried. Ellmann, Lawrence and Thorold [167] report their observations of 90 patients divided into experimental and control groups. Their results show that large doses of gold salts lead to inactive phases of the disease. In 47 per cent of those receiving large doses and 27 per cent of those receiving small doses the disease became inactive. Sixty-six per cent of those receiving large doses and 59 per cent of those receiving small doses showed reduced swelling about the infected joint. However, although according to most authors gold preparations make rheumatoid arthritis inactive in a large percentage of the cases, they are dangerous drugs because they seriously damage the kidneys, the intestines, and the skin and have caused deaths. Some physicians have felt it necessary to safeguard themselves by requiring patients to sign their release from all responsibility for the possible complications.[168]

Gold is excreted slowly and may not have left the body even six months after its administration has been discontinued. Its use should be stopped when the sedimentation rate is below 12 mm.[167] [ED. NOTE: Carefully controlled experiments are being carried out in many clinics to find if possible the correct way to use gold salts.]

Sulfur Treatment.—This form of treatment has lost favor during the last year. Freyberg, Block and Fromer,[169] Abrams and Bauer [170] and Cawadias [171] have found no sulfur deficiency and see no need for its use. Freyberg has even suggested that the treatment might be harmful.[169]

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165. (*a*) Sabin, A. B., and Warren, J.: Therapeutic Effectiveness of Practically Non-Toxic New Compound (Calcium Aurothiomalate) in Experimental, Proliferative, Chronic Arthritis of Mice, Science **92**:535-536 (Dec. 6) 1040. (*b*) Driscoll, R. E., and Markson, D. E.: One Hundred Cases of Arthritis Treated with Comparatively Non-Toxic Gold Compound, Illinois M. J. **78**:503-504 (Dec.) 1940. (*c*) Hansen, A. C.: Treatment of Atrophic Arthritis, Wisconsin M. J. **39**: 106-108 (Feb.) 1940. (*d*) Hoegh-Guldburg. [164d]

166. Secher, K.: Vitamins as Supplement to Sanocupin in Arthritis, Lancet **1**:735-736 (April 20) 1940; Sanocupin and Vitamin C in Therapy of Arthritis and Tuberculosis, Nord. med. (Hospitalstid.) **6**:821-832 (April 27) 1940.

167. Ellmann, P.; Lawrence, O. S., and Thorold, G. P.: Gold Therapy in Rheumatoid Arthritis, Brit. M. J. **2**:314-316 (Sept. 7) 1940.

168. Comroe, B. I.: Arthritis and Allied Conditions, Philadelphia, Lea & Febiger, 1940.

169. Freyberg, R. H.; Block, W. D., and Fromer, M. F.: Study of Sulfur Metabolism and Effect of Sulfur Administration in Chronic Arthritis, J. Clin. Investigation **19**:423-435 (March) 1940.

170. Abrams, N. R., and Bauer, W.: Treatment of Rheumatoid Arthritis with Sulfur: Critical Evaluation, New England J. Med. **222**:541-546 (March 28) 1940.

171. Cawadias, A. P.: Sulphur Treatment in Endocrine Metabolic Arthropathies, Brit. J. Rheumat. **2**:125-129 (Jan.) 1940.

Wheeldon,[172] however, still finds sulfur as used in his clinic of real value.

Sulfanilamide Treatment.—Sulfanilamide appears to be effective only in gonorrheal arthritis; it does not help in other types.[173]

Treatment with Vitamins.—There is increasing proof of general vitamin deficiency in chronic rheumatoid arthritis. Hall, Bayles and Soutter[174] have seen no improvement after eight months of use of vitamin A. The requirements of patients with rheumatoid arthritis were found to be four to ten times the normal amount in the diet. Opinions vary as to the use of vitamin D. Muether[175a] considers it dangerous. Snyder and Squires[176] believe it beneficial when given in large doses. The vitamin B complex and vitamin C have been found useful.[175] Jacques[177] feels that vitamin C has no effect on rheumatoid arthritis.

Roentgen Treatment.—This form of treatment has for many years been successfully used by Kahlmeter, of Stockholm, who claims excellent results.[178] His work has stimulated its use in this country. In spite of many studies no one yet knows to just what the beneficial effects are due. Smyth, Freyberg and Peck[179] treated 100 patients. The majority of these had characteristic rheumatoid arthritis; others had rhizomelic spondylitis, degenerative disease of joints or so-called fibrositis. They were given roentgen therapy to some of the joints. For the most part,

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174. Hall, M. G.; Bayles, T. B., and Soutter, P.: Vitamin A Requirements in Rheumatoid Arthritis, New England J. Med. **223**:92-96 (July 18) 1940.

175. (*a*) Muether, R. O.: Use of Vitamins in Chronic Arthritis, J. Missouri M. A. **37**:111-114 (March) 1940. (*b*) Wille, E.: Vitamin C and B_1 in Arthritis, Fortschr. d. Therap. **16**:118-122 (April) 1940.

176. Snyder, R. G., and Squires, W. H.: Preliminary Report on Activated Ergosterol: Form of High-Dosage Vitamin D in Treatment of Chronic Arthritis, New York State J. Med. **40**:708-719 (May 1) 1940.

177. Jacques, R. H.: Relation Between Reduced Ascorbic-Acid Levels of Blood Plasma and Rheumatoid Arthritis, J. Bone & Joint Surg. **22**:324-326 (April) 1940.

178. Kahlmeter, G.: Chronic Rheumatic Diseases, edited by C. W. Buckley, New York, The Macmillan Company, 1937, p. 17.

179. Smyth, C. J.; Freyberg, R. H., and Peck, W. S.: Experiences with Roentgen Therapy in Various Rheumatic Conditions, J. A. M. A. **115**:2209-2210 (Dec. 21) 1940.

patients were selected who had pairs of comparably affected joints, and roentgen treatment was applied to only one of the pair, the untreated joint serving as a control. In still other cases the possible psychic effect of such treatment was studied by screening some joints with lead so that no roentgen rays reached the skin. The effect of such treatment was measured by careful study of the subjective response, observation of physical changes at the joints, frequent determinations of the erythrocyte sedimentation rate, diagnostic roentgen examinations of the joints and noting of changes in synovial fluid from both treated and untreated joints before and after roentgen therapy and in several cases by microscopic study of joint capsule and synovial biopsy tissue.

Results were not encouraging. Rheumatoid arthritis was not improved; spondylitis was most benefited. Pain was relieved, but improvements might be due to psychic effects. Cases were observed for only eighteen months in this series. Holbrook [180] agrees with Freyberg and his co-workers.

Swaim [180] stresses the point that the treatment is local only. The sedimentation rate was therefore not changed in his cases; no changes in the roentgenograms were noted. He believes decrease of pain is the first beneficial result and lessened spasm the second. Since 1932, 164 patients have been treated: 85 with rheumatoid arthritis, 31 with osteoarthritis, 28 with these two forms combined and 18 with Strümpell-Marie arthritis. Swelling decreased, and limited motion improved. Recalcification was observed, as has been reported before. No ill effects have been reported. Ninety per cent of those in whom the swelling and pain in the joints had been of six months' duration or less were improved. Best results are had when treatment is instituted early. Children respond especially well. Frequent small doses continued for a long time give better results than larger doses at longer intervals. Improvement occurs only after a year.

Leddy [180] observes that since arthritis is a chronic inflammatory disease high voltage and large doses are unnecessary. It is worth trial for relief of pain. Freund [180] has had good results. Freiberg (J. A.) [180] is doubtful of the results and feels there is danger due to osteoporosis. Ochsner and Mumford,[181] Weinberg,[182] Saralegni [183] and Jovin [184] report

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180. In discussion on Smyth, Freyberg and Peck.[179]

181. Ochsner, H. C., and Mumford, E. B.: Roentgen Therapy for Painful Conditions of Bones and Joints, Radiology **34**:444-445 (April) 1940.

182. Weinberg, T. B.: Arthritis and Para-Arthritis Treated with the Roentgen Ray: Report of One Hundred and Sixty-One Cases, Am. J. Roentgenol. **43**:416-424 (March) 1940.

183. Saralegni, J. A.: Technique and Results of Deep Radiotherapy in Chronic Rheumatism, Rev. Asoc. méd. argent. **53**:1095-1097 (Dec. 15) 1939.

184. Jovin, I.: Limits and Possibilities of Roentgenotherapy in the Treatment of Articular Rheumatism, Gaz. méd. de France (supp. Cah. radiol.) **47**:122-127 (Jan. 15) 1940.

permanent improvement in both types of arthritis. [ED. NOTE: The best technic apparently has not yet been developed or the treatments controlled enough to give constant results. However, roentgen treatment seems to do no harm and should be investigated further.]

Prevention of Deformity.—The orthopedic surgeon is chiefly responsible for two aspects of the treatment of chronic arthritis, the prevention of deformity and the correction of deformity. The prevention of deformity is possible if the patients are seen early and the joints are adequately splinted. Bell [185] says the importance of prevention of deformity cannot be overemphasized. Splinting is the means recommended; it is easily done and is almost always successful. It should be done early, since deformity once established is most difficult to correct. The fear that immobilization will result in a stiff joint is unfounded; movement aggravates the inflammatory process. Light plaster splints or bivalved casts are to be used as indicated. Atrophic arthritis causes most of the deformities. Persistent flexion causes contractures of the capsule and muscles and results in deformities. This does not happen in hypertrophic joints. Splinting as a form of preventive treatment is now universally recommended. Tippett,[186] Stump,[187] Ruiz Moreno and Tarnopolsky,[188] Cecil,[189] Swaim,[190] Haden [191a] and Hill,[191b] all advise its use.

Another means of preventing deformity is physical therapy. Correct posture must be stressed. It is necessary for recovery and prevention of further trouble. Krusen [192] stresses three procedures: (1) heat and cold water and electrical measures; (2) mechanical aids, such as massage and manipulation, as well as splinting; (3) exercise, position and rest. He recommends especially rest with the joint in position to prevent

185. Bell, B. T.: Prevention and Correction of Deformities in Arthritis, M. Clin. North America **24**:1735-1743 (Nov.) 1940.

186. Tippett, G. O.: Use of Plaster Splintage in Treatment of Arthritis, Brit. J. Rheumat. **2**:195-202 (April) 1940.

187. Stump, J. P.: Prevention of Arthritic Deformities by Early Orthopedic Management, Ann. Int. Med. **14**:87-99 (July) 1940.

188. Ruiz Moreno, A., and Tarnopolsky, S.: Relation Between Orthopedics and Rheumatism, Día méd. **12**:162 (Feb. 26) 1940.

189. Cecil, R. L.: Physical Therapy Compared with Other Measures in Arthritis, Arch. Phys. Therapy **21**:581-584 (Oct.) 1940.

190. Swaim, L. T.: Physical Therapy in Arthritis, Public Health Nursing **32**:246-247 (April) 1940.

191. (*a*) Haden, R. L.: Rheumatoid Arthritis: Etiology and Treatment, Arch. Phys. Therapy **21**:671-677 (Nov.) 1940. (*b*) Hill, L. C.: Observations on Treatment of Rheumatoid Arthritis, Brit. J. Rheumat. **2**:202-207 (April) 1940.

192. Krusen, F. H.: Physical Treatment of Arthritis, Arch. Phys. Therapy **21**:144-153 (March) 1940; Physical Therapy in Arthritis with Special Reference to Home Treatment, J. A. M. A. **115**:605-615 (Aug. 24) 1940.

contracture and deformity. Mobilization should be induced by degrees under adequate supervision.

Wyman [193] recommends under-water exercises in walking. Cecil [189] and Swaim [190] feel that physical therapy is one of the most important measures in the treatment of chronic arthritis but that it should be supervised by a specialist. Martucci [194] describes the physical agents used in the treatment of arthritis, including baking, diathermy, paraffin baths for the hands and feet, mud packs and massage to delay muscle atrophy, restore the tissues, improve the local metabolism, increase circulation and prevent muscle contraction. Hydrotherapy, exercise and rest are also mentioned. Massage, active and passive exercises and muscle training in posture correction are most important [195] and should be followed by occupational therapy, which is of great value physically as well as mentally. Home work should be planned,[196] as it is vitally important to maintain the morale.

Correction of Deformity.—The correction of deformity can be accomplished by slow manipulation and frequent changes of casts as the relaxation takes place. Frequently, however, a reconstructive operation is necessary both for rheumatoid arthritis and for hypertrophic hips.[197] Bell [185] states that when the joint has been quiescent for from three to six months operation may be used to correct deformities after the muscles have been strengthened. Manipulation, active exercises and splints are

193. Wyman, J. F.: Advantages of Institutional Care and Physical Therapy in Chronic Arthritis, Arch. Phys. Therapy. **21**:301-304 (May) 1940.

194. Martucci, A. A.: Physical Therapy in the Treatment of Chronic Arthritis, M. Clin. North America **24**:1685-1696 (Nov.) 1940.

195. Kullberg, R. W., and Lowell, L. M.: The Physiological Approach to Rheumatoid Arthritis, Rocky Mountain M. J. **37**:114-116 (Feb.) 1940. Kendrick, J. I.: Physical Therapy Principles of Peri-Arthritis of the Shoulder, Arch. Phys. Therapy **21**:41-44 (Jan.) 1940. Hamilton, J. F.: Use and Misuse of Physical Therapeutics in Treatment of Arthritis, Memphis M. J. **15**:184-187 (Nov.) 1940. Frazier, V. E.: Underwater Therapy in Chronic Arthritis, J. Missouri M. A. **37**:192-193 (May) 1940. Kahlmeter, G.: Treatment of Arthrosis and Spondylosis with Therapeutic Gymnastics, Nord. med. (Hygiea) **5**:343-346 (Feb. 24) 1940. Hummel, R.: Therapeutic Exercises with Elimination of Pain by the Intravenous Strontium Bromide Injections and Contribution to Roentgenotherapy, Med. Welt **13**:1533-1534 (Dec. 2) 1939. Fletcher, G. B.: Underwater or Pool Treatment of Certain Conditions of Muscles, Nerves and Joints, Tri-State M. J. **12**:2411 (Jan.) 1940. Sherwood, K. K.: Physical Therapy in Arthritis, Physiotherapy Rev. **20**:134-137 (May-June) 1940.

196. Bell, C., and Swaim, L. T.: Occupational Therapy in Arthritis, Pub. Health Nursing **32**:243-245 (April) 1940. Pattee, G.: Prescribed Exercises to Be Carried Out at Home: Home Occupational Therapy, Occup. Therapy **19**:169-175 (June) 1940. Elliston, W. A.; Silber, M. F., and Grover, D.: Physiotherapy in Rheumatoid Arthritis, New England J. Med. **224**:150-156 (Jan. 23) 1941.

197. Charry, V.: Role of the Practitioner in Orthopedic and Surgical Therapy of Chronic Rheumatism, Monde méd. **49**:828-831 (Nov.) 1939.

effective when the condition is mild. Manipulation with the patient under an anesthetic may be used but is dangerous in cases of rheumatoid arthritis. Wedge casts are good for correcting deformities of the joints of extremities. Lengthening of the tendons and capsulotomy are of value when the knee is subluxated. Removal of the synovial membrane is a valuable procedure when there is chronic hypertrophic synovitis. Resection of the patella is performed when movement of the patella is limited. Cheilotomy helps when osteophytes form a block to movement. Arthroplasty is of value in cases of ankylosis of the hip, knee or elbow. When only one weight-bearing joint is badly damaged, arthrodesis is satisfactory, as it produces a painless, stable extremity. Osteotomy is valuable in correcting bony ankylosis in a deformed position.

Pfeiffer and Bach [198] feel that all patients must be thoroughly studied and the essential medical measures carried out. Splinting and corrective and muscle-setting exercises must be used prior to surgical intervention. Operation is best only after the disease has been inactive for at least a year. Synovectomy is used when the usual supportive measures have not been satisfactory and the persistent pathologic changes are confined to the synovia. It restores the range of motion to from 90 degrees to normal, depending on the case, and makes walking possible. Posterior capsuloplasty may be used when there is little damage to the cartilage. Sometimes a combination of the two operations is recommended. The follow-up by surgeon and internist is important.

Ghormley and Cameron [199] report 103 synovectomies in 88 patients, 14 bilateral. The operation is best adapted to the knee joint. Of 90 cases with synovitis, in 34.4 per cent the result was excellent, in 33.3 per cent there was improvement, and in 32.2 per cent the result was poor.

All patients with traumatic arthritis, osteochrondromatosis, xanthoma and hypertrophic arthritis were cured or improved. Of the patients with chronic synovitis, 77.4 per cent were cured or improved; of those with chronic infectious arthritis, 56.2 per cent, and of those with synovitis which later developed into chronic infectious arthritis, 54.9 per cent. In discussing this, Swett [200] shows that in 24 of 52 cases of atrophic arthritis there was improvement or an excellent result. His figure agrees with the contention of Inges that synovectomy offers 50 per cent improvement to one-half the patients with atrophic arthritis. He feels that the

198. Pfeiffer, D. B., and Bach, T. F.: Reconstructive Surgery in Chronic Rheumatoid Arthritis, M. Clin. North America **24**:1745-1753 (Nov.) 1940.

199. Ghormley, R. K., and Cameron, D. M.: The End Results of Synovectomy of the Knee Joint, J. A. M. A. **115**:2208-2209 (Dec. 21) 1940.

200. In discussion on Ghormley and Cameron.[199]

conditions under which synovectomy can be expected to yield a high percentage of good results depend on the type of disease and the stage of the process. One must remember that the operation is applicable only to (1) a synovial proliferative process, (2) increase of the perichondrium, endosteum and epiphysial connective tissue and (3) sites where capsular fibrous or muscular fibrous tissue is predominant. Therefore, patients with synovial involvement must be operated on as soon as proliferation is found not to undergo spontaneous resolution before it has caused damage to the structure of the joint, and before protracted invalidism has caused depletion.

Failures are due to the fact that operation is performed in cases of other than synovial involvement or to tardiness in operating. Dickson,[200] reporting on 140 synovectomies, says that proper removal of synovia and other material from an infected joint results in improvement in other joints in a large percentage of cases. It cannot be ignored that failures are traceable to incomplete operation. Disintegrated semilunar cartilages, all destroyed cartilages, all hypertrophic osteophytes, all pannus and projecting hypertrophic margins must be removed to obtain good results.

Key [200] agrees that radical synovectomy should be done early in cases of presumable rheumatoid arthritis. Ghormley [199] believes that it is most important to select the cases and perform radical operations and later manipulate for three or four weeks.

Henderson and Pollock [201] report 77 cases of osteoarthritis of the hip joint. Men predominated over women among the patients, 55 to 22. The authors state: "From the point of view of therapy, undoubtedly, arthrodesis as performed by us has given the best results, but, while this is a procedure which is readily accepted in Europe, in America we have difficulty in convincing our patients of the benefits to be derived from a stiff hip. . . . Of the other procedures, each has its place in well-selected cases. Drilling, combined with manipulative measures and followed by active movements, aided by physical therapeutic agents, has given good results in many cases. The more recent work of Smith-Petersen with vitallium caps in arthroplasty of the hip joint bids fair to change our views on this operation, but, until further experience has been gained, the procedure is still *sub judice*." Acetabuloplasty and extensive cheilotomy give excellent results in some cases.

Lewis and Graham [202] stress the importance of extreme care in handling fractures of the ankle because of the secondary osteoarthritis which may result and is crippling.

(To Be Continued)

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201. Henderson, M. S., and Pollock, G. A.: Surgical Treatment of Osteo-Arthritis of Hip Joint, J. Bone & Joint Surg. **22**:923-931 (Oct.) 1940.

202. Lewis, R. W., and Graham, W. C.: Secondary Osteoarthritis Following Fractures of the Ankle, Am. J. Surg. **49**:210-218, (Aug.) 1940.